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VOLUME 56

JULY-DECEMBER, 1948

ST. LOUIS
THE C. V. MOSBY COMPANY
1948

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*Printed in the
United States of America*

*Press of
The C. V. Mosby Company
St. Louis*

American Journal of Obstetrics and Gynecology

VOL. 56

JULY, 1948

No. 1

*Transactions of the Central Association
of Obstetricians and Gynecologists. Annual Meeting Held
October 23 to 25, 1947, at Louisville, Kentucky*

THE EFFECTIVENESS OF VARIOUS DIURETIC AGENTS IN CAUSING SODIUM EXCRETION IN PREGNANT WOMEN*

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TOXEMIA of late pregnancy remains the one large cause of maternal morbidity and mortality for which there is no adequate etiologic explanation. Many students doubt that it is a single disease entity and differential classifications have been offered to explain the variety of clinical manifestations. In spite of the extended investigative efforts that have been expended on this syndrome, it still remains a therapeutic enigma, our ministrations being quite empirical.

Edema is one of the most common signs of toxemia, and yet it is not clear whether the accumulation of fluid represents a disorder of water or sodium or protein metabolism. Earlier workers focused attention on water metabolism and treated such patients by manipulations of water intake. Limited investigations in this direction have been complicated by the difficulties in obtaining proper control. During the past two decades the concept that edema may be due to a disorder of sodium metabolism has gained popularity to the extent that the clinical management of toxemias of pregnancy now generally includes a reduction in sodium intake (sodium chloride and sodium bicarbonate).

*Read before Central Association of Obstetricians and Gynecologists on Oct. 23, 1947, at Louisville, Ky.

Because of the interest in sodium and in the factors involved in augmenting its excretion, a series of studies was undertaken to investigate the effects of so-called diuretic agents on the fluid and sodium excretion in women with normal and toxemic pregnancies.

Water balance studies require a long-time control of intake and output, including the insensible loss of water through respiration and perspiration. Because of these difficulties, several investigators have attempted to study sodium balance. In general, the methods of sodium analysis have been too cumbersome for routine laboratory determinations. Consequently, more work has been done on chloride balance studies on the assumption that there is a definite relation between chloride and sodium. This is obviously incorrect since not all the chloride in the urine and food is sodium chloride. In addition, attempts have been made to investigate the effect of ammonium chloride, where the excess chlorides make chloride estimations entirely unreliable as an index of sodium excretion. A simplified method of sodium estimation developed in this laboratory made it possible to study the effect of various diuretics on sodium output.

Observations were made on pregnant patients given high and low sodium diets. Hourly fractional or total twenty-four-hour urine specimens were obtained and determinations made of the sodium concentration in the urine. From these data, information regarding the mobilization and excretion of sodium have been obtained which may have some direct application in the clinical management of edema of pregnancy.

Methods and Materials

Sodium Method.—There are two basic methods for measuring the sodium content of biologic materials. The physical method makes use of a flame photometer.¹ The substance to be measured is dissolved and burned at a constant volume rate. The intensity of the sodium flame is measured and computed as grams of sodium. While this method has many advantages, the operation of the flame photometer is such a highly technical procedure that its use is not satisfactory for most laboratory technicians.

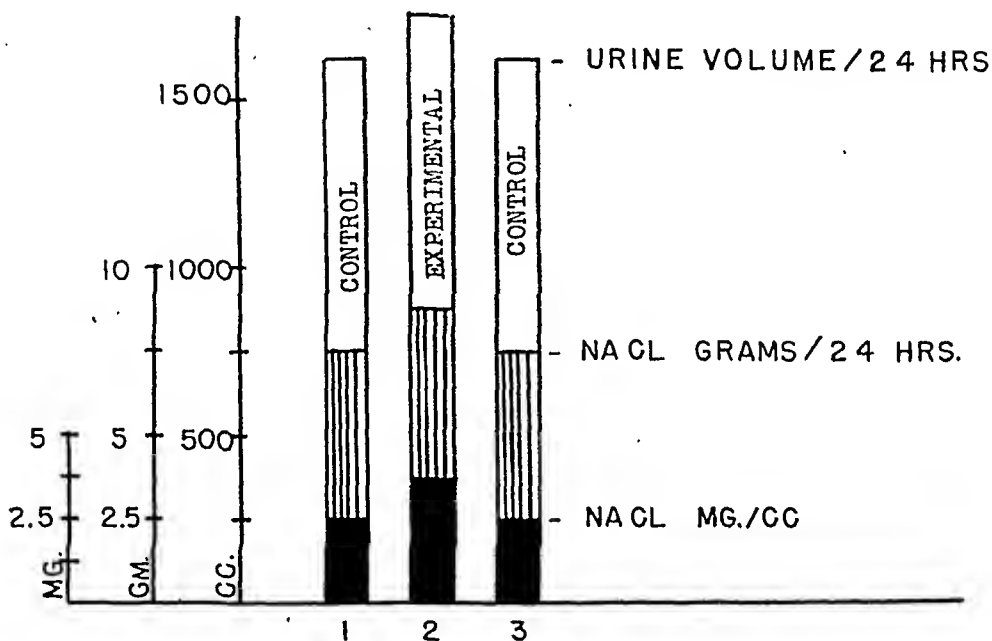
The chemical method involves the precipitation of sodium by uranyl zinc acetate.² The quantity of sodium in the precipitate can be determined by gravimetric or colorimetric procedures.

The sodium determinations in this study were made by a colorimetric technique based on the original gravimetric method. When the triple salt, uranyl zinc sodium acetate is precipitated, the reagent solution loses color in proportion to the amount of uranyl ions lost from solution. The loss of color is measured by an electrophotometer and its sodium equivalent is determined from a standard reference curve.³ In this report all values for sodium are expressed in terms of sodium chloride; the conversion to sodium can be obtained by multiplying all figures by 0.4.

Patient Control.—The patients used in this study were hospitalized in the obstetric wards. Their diets were prepared by the Department of Nutrition and the caloric values and sodium contents calculated from tables. These diets have been varied from low values of 1 to 1.5 Gm. of sodium chloride (0.4 to 0.6 Gm. sodium) per twenty-four hours to normal values of 4 to 6 Gm. per twenty-four hours; higher intakes of 10 to 15 Gm. were achieved by giving the patients additional salt.

The patients were housed in a special ward and their water intake recorded daily. The studies were continued over periods of several weeks. Each patient was given a controlled sodium intake for a minimum of three and usually five days prior to establishment of a treatment schedule. The experimental schedules were generally arranged to correspond to the usual clinical therapeutic plans employed in the hospital. Observations were made on normal and toxemic pregnant patients and on a few nonpregnant women in the childbearing age.

Urine was collected daily as a twenty-four-hour specimen and the sodium content of each was determined. The average values for the specimens three days prior to, and three days following treatment were used as controls and compared with the urine volume and sodium value obtained on the day of the test.



Key to figures:

1. Pretreatment control (1 day or average of 3 days)
2. Day of treatment
3. Post-treatment control (1 day or average of 3 days)

The figures illustrating the text are constructed in the same way as this sample graph.

Materials Studied.—The following substances were selected and studied for their effect on the excretion of water and sodium.

1. Water (by mouth) given in quantities of 2,000 to 6,000 c.c. daily. A few patients received this amount of water in two to four hours.
2. Dextrose (intravenously); given as 5 per cent, 10 per cent, 25 per cent and 50 per cent solutions in amounts varying from 400 to 4,000 c.c. depending upon the concentration.
3. Aminophylline (intramuscularly); given in doses ranging from 120 mg. to 150 mg. daily (1 gr. b.i.d. to 7½ gr. t.i.d.).
4. Mercurial diuretics (Salyrgan (100 mg./c.c.), Salyrgan-theophylline (mercurial 100 mg./c.c. plus theophylline 50 mg./c.c.) and Mereuhydrin (mercurial 88 mg./c.c. plus theophylline 48 mg./c.c.) given intravenously in doses ranging from 2 to 4 c.c.).
5. Ammonium chloride (by mouth and intravenously); given in amounts varying from 8 to 16 Gm. per 24 hours,

6. Urea (by mouth); given in amounts of 60 Gm. per 24 hours (20 Gm. in 80 c.c. of water t.i.d.).

All of these substances have some effect on sodium and/or water excretion. The effect varies with the diuretic but each agent follows a fairly consistent pattern.

Data

Effect of Dietary Sodium on Urinary Sodium Excretion.—When patients entered the hospital having been on an unregulated diet, it was found that their sodium excretion usually ranged from 8 to 10 Gm. per twenty-four hours. When placed on bed rest and given a general hospital diet, their urinary sodium content dropped slightly during a three- to five-day interval and stabilized at 6 to 8 Gm. per twenty-four hours.

The effect of changes in the level of sodium intake was observed in one patient who was given 10 Gm. of salt daily in addition to her diet. It is apparent in Fig. 1 that there was a lag of three to five days before the sodium excretion reached the level of intake after the extra salt was given and again after it was discontinued. This exemplifies the need for maintaining a known sodium intake to evaluate the significance of changes in sodium excretion.

Effect of Forcing Fluids on Urinary Sodium.—It is customary in this clinic for all patients presenting evidence of toxemia of late pregnancy to be given a low salt diet and to receive fluids up to 4,000 c.c. daily. To check the effect of this schedule, normal pregnant women were placed on a similar regimen. In some patients, 6,000 c.c. of water were given orally in two to three hours to see if any augmentation in sodium excretion could be obtained. The effect of such fluid intake on sodium and urine excretion was noted and these data are illustrated in Fig. 2. It is apparent that urinary output can be increased by augmented fluid intake, but the excretion of sodium was decreased during the day of forced fluids. Not only was the concentration of sodium per liter of urine reduced, but the twenty-four-hour sodium output was also diminished. It made little difference whether the fluid was given in two to three hours or over the twenty-four-hour period. These findings are in accord with earlier reports that chloride excretion may be reduced by forcing fluids.

To check this effect 2,000 to 4,000 c.c. of fluids were given by vein. In these patients, there was also a slight decrease in urinary sodium concentration but the greatly increased urine volume produced a slight increase in the total sodium excreted in twenty-four hours, Fig. 3. There is a difference in the amount of sodium excreted whether the fluids are given by mouth or by vein.

The Effect of Intravenous Dextrose on Sodium Excretion.—To determine whether this apparent advantage of intravenous fluid in increasing sodium excretion was due to the dextrose or to the fluid, studies were undertaken to measure these factors. Two hundred grams of dextrose were given intravenously in 4,000 c.c. (5 per cent), in 2,000 c.c. (10 per cent), in 800 c.c. (25 per cent), or in 400 c.c. (50 per cent) (as rapidly as clinically feasible). The process was then reversed and the volume injected was held constant: the patients were given 400 c.c. of each solution, 5 per cent, 10 per cent, 25 per cent, or 50 per cent dextrose. The experimental day was measured from the onset of the infusion, usually from 8 A.M. to 8 A.M.

The twenty-four-hour urinary excretions obtained under these conditions are recorded in Figs. 3 and 4. When 200 Gm. of dextrose were given as 400 c.c. of a 50 per cent solution, there was usually a retention of sodium during the

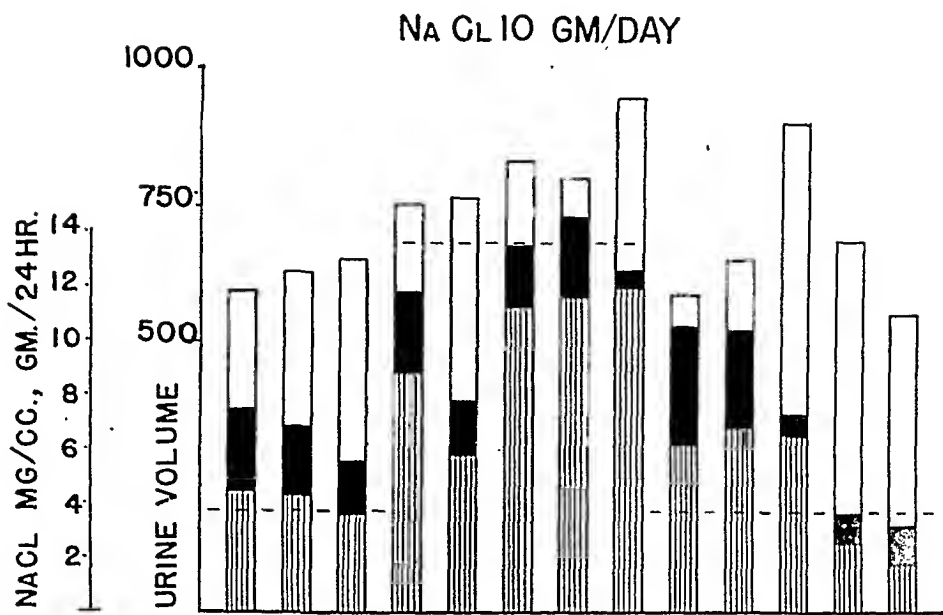


Fig. 1.—Graphic representation of the daily excretion of urine and sodium when the salt in the diet (3.8 Gm.) was augmented by giving an additional 10 Gm. a day for five days.

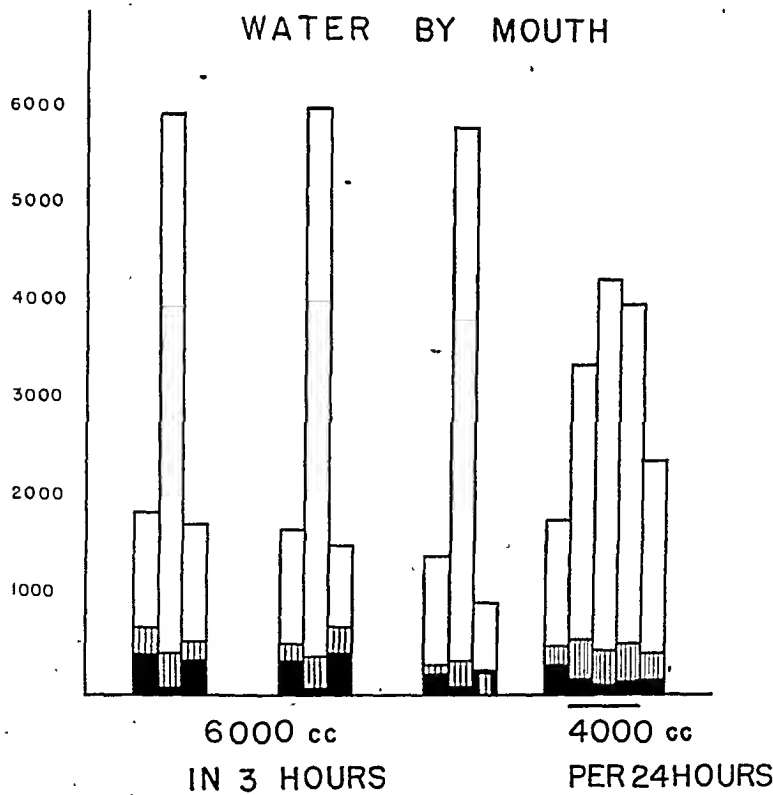


Fig. 2.—Graphic representation of the excretion of urine and sodium when fluids were given by mouth, 6,000 c.c. for one day, and 4,000 c.c. for three successive days.

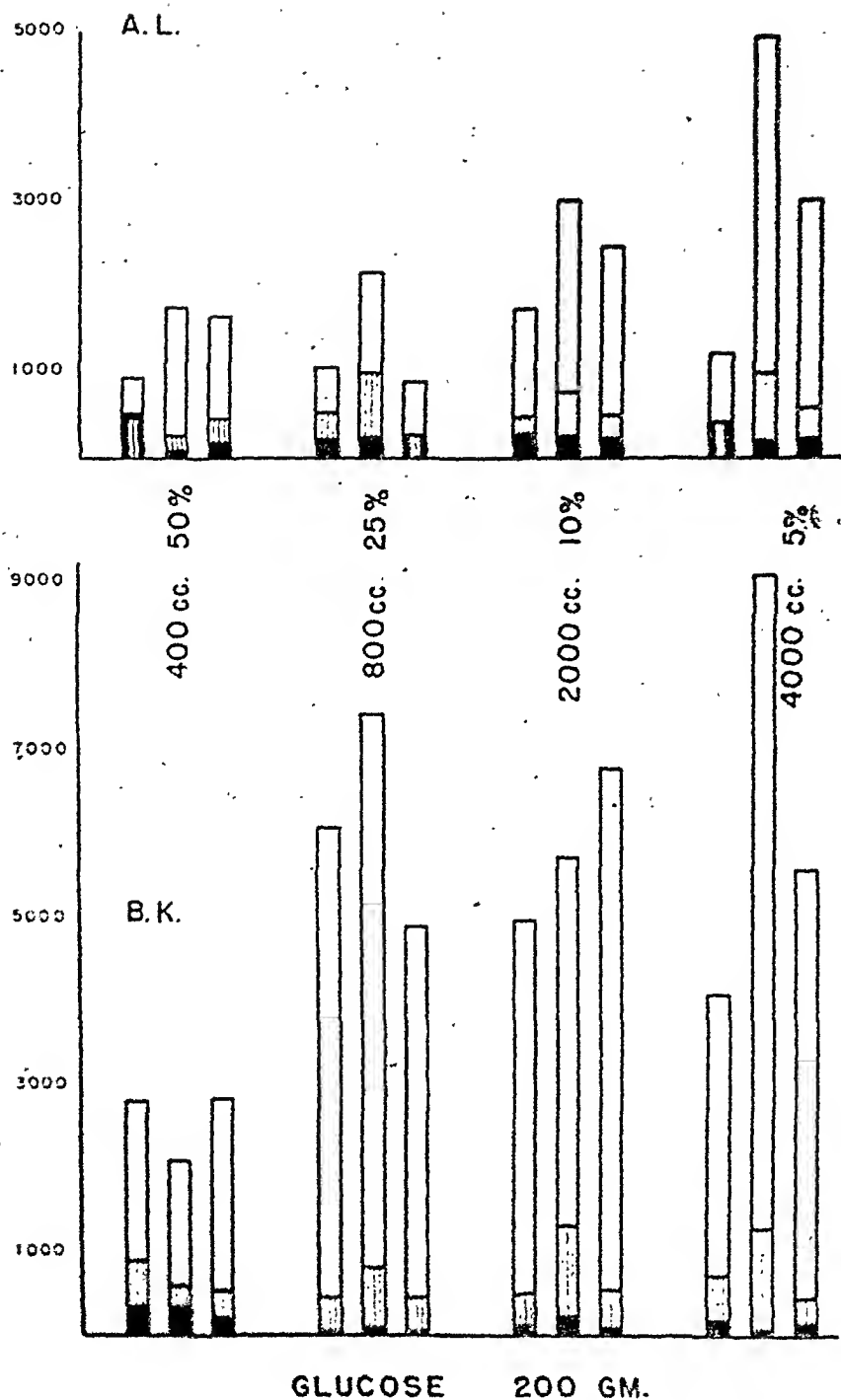


FIG. 3.—Graphic representation of the excretion of urine and sodium in two patients who were given intravenous solutions containing 200 Gm. of glucose (dextrose). The interval between these observations was five to seven days. The polydipsia and polyuria of B. K. lasted for about five weeks, but the effect of infusions of dextrose was still the same as in other patients.

twenty-four hours. As the volume of fluid was increased and the concentration of dextrose decreased, there was a progressive but slight increase in the twenty-four-hour sodium excretion so that the 200 Gm. of dextrose given as 4,000 c.c. of a 5 per cent solution produced a definite and consistent increase in sodium output. When the volume of injected dextrose was constant, there was no

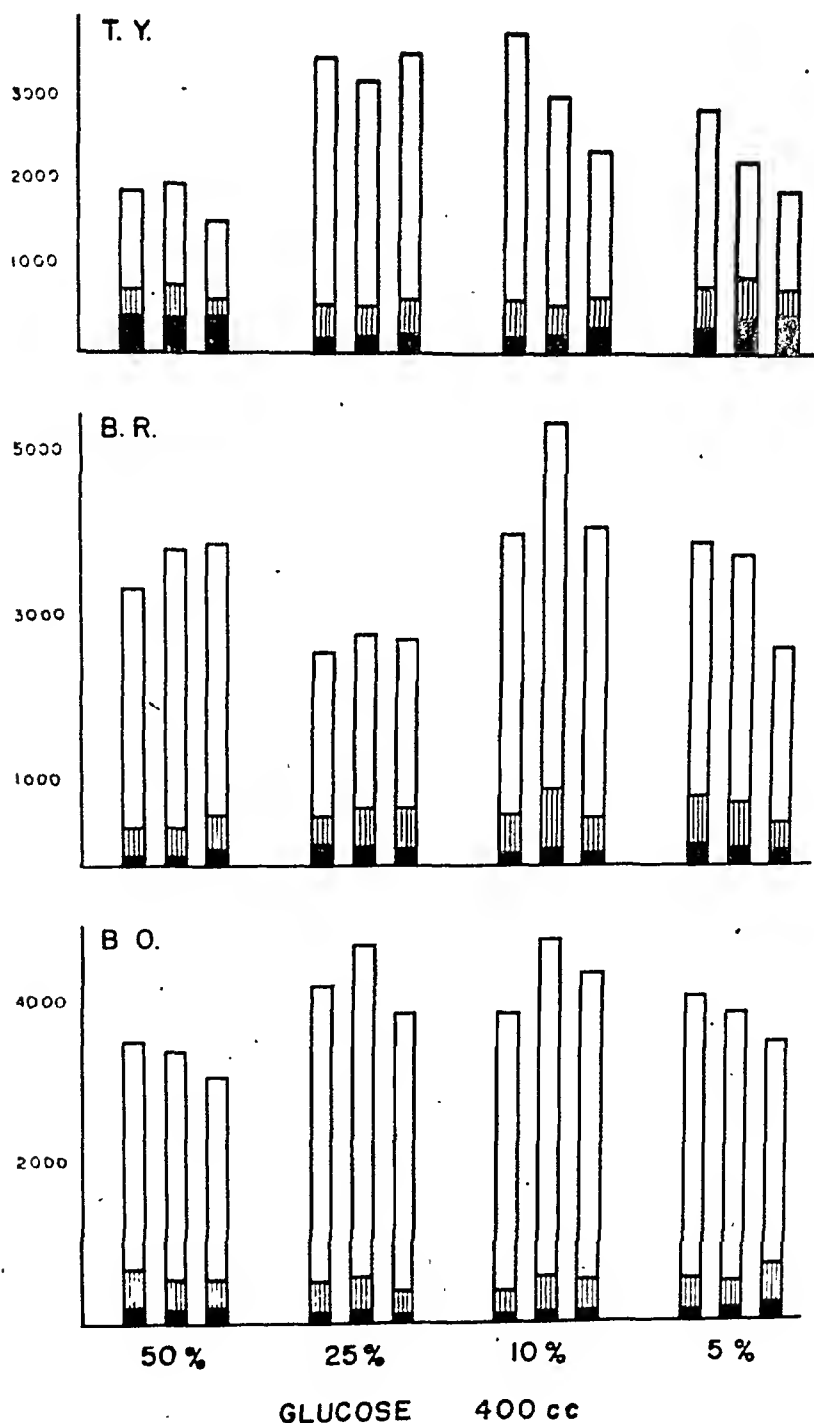


Fig. 4.—Graphic representation of the excretion of urine and sodium when patients were given 400 c.c. of glucose (dextrose) solutions intravenously. The interval between the injections in these three patients varied from five to seven days. There is no demonstrable effect on urine or sodium output even though the dose of dextrose varied from 20 to 200 Gm.

change in the urinary sodium output as the concentration of dextrose varied from 5 to 50 per cent. Thus it makes no difference whether 20 or 200 Gm. of dextrose is added to the 400 c.c. infusion when the total twenty-four-hour urinary volume or sodium is considered. Since any diuretic effect of a crystalloid is transitory, similar hourly fractional studies of sodium excretion were undertaken to ascertain whether an initial diuretic effect had been missed in the total twenty-four-hour sample. Eight hundred cubic centimeters seemed the maximal amount that could safely be introduced into the blood stream within two hours. The patients' schedules were arranged to provide urine samples at two-hour intervals from 8 A.M. to 8 P.M. Indwelling urethral catheters were employed to insure that the bladder was emptied at the end of each two-hour interval. The overnight specimens were pooled. Urine samples were obtained in this manner for three successive days. Eight hundred cubic centimeters of 5 per cent or 25 per cent dextrose were given intravenously on the second day. (Fig. 5.) In each instance, there was a marked increase in urine during the period of infusion but in neither case did the urine output equal the amount of fluid injected. In the two-hour fractions, the sodium content and concentration were decreased but the twenty-four-hour output of sodium was not altered by either solution. The addition of dextrose to intravenous fluids does not seem to augment the diuretic effect of the water which carries it when measured by urine volume. This is found in both fractional and pooled twenty-four-hour specimens.

The administration of 500 c.c. of 25 per cent dextrose was followed by a diminished urine and sodium excretion (Fig. 5). The oliguric phase which follows the administration of a hypertonic solution has been shown to be due to the release of the antidiuretic hormone from the posterior pituitary.⁴ This antidiuretic effect of hypertonic solutions detracts from their use as diuretic agents.

The Effect of Aminophylline on Sodium Excretion.—Aminophylline has not been extensively used in the treatment of edema of pregnancy, and very few data are available regarding its effect on sodium excretion. Most reports deal with the effect of aminophylline in conjunction with other diuretic agents and the effects are measured in terms of total urinary volume or of the decrease in weight of edematous patients. To study the effect of aminophylline alone as well as in conjunction with other agents, it was first given separately. A series of patients was given aminophylline intramuscularly in doses ranging from 1 grain b.i.d. to $7\frac{1}{2}$ grains t.i.d. (120-1,500 mg. daily). The smaller doses of aminophylline had no measurable effect on the patient, the urinary volume, or on sodium excretion. When patients were given $7\frac{1}{2}$ grains t.i.d. intramuscularly, vomiting occurred frequently. It is apparent that vomiting associated with aminophylline administration is central in origin. Despite this loss of sodium intake due to the vomitus, there was a marked increase in urinary sodium. This increase in urinary sodium was obtained primarily by an increase in sodium concentration in the urine. No evidence is available from these studies to explain the mechanism of the increase in sodium concentration in the urine (Fig. 6).

The Effect of Mercurials on Sodium Excretion.—Salyrgan was obtained without theophylline and injected intravenously into a series of patients at seven or eight o'clock in the morning in doses ranging from 2 to 4 c.c. (200 to 400 mg.). This mercurial caused a marked increase in urinary sodium and volume. This increase in sodium is due largely to an increased concentration in the urine (Fig. 7). The degree of increased sodium excretion varies with the dosage of mercurial administered. A dose of 2 c.c. was frequently ineffective

in increasing the urinary volume or total sodium excretion while 3 or 4 c.c. was consistently effective.

On the day following this marked output of sodium, there was a transient retention of sodium as manifested by a sharp drop in urinary sodium per twenty-four hours.

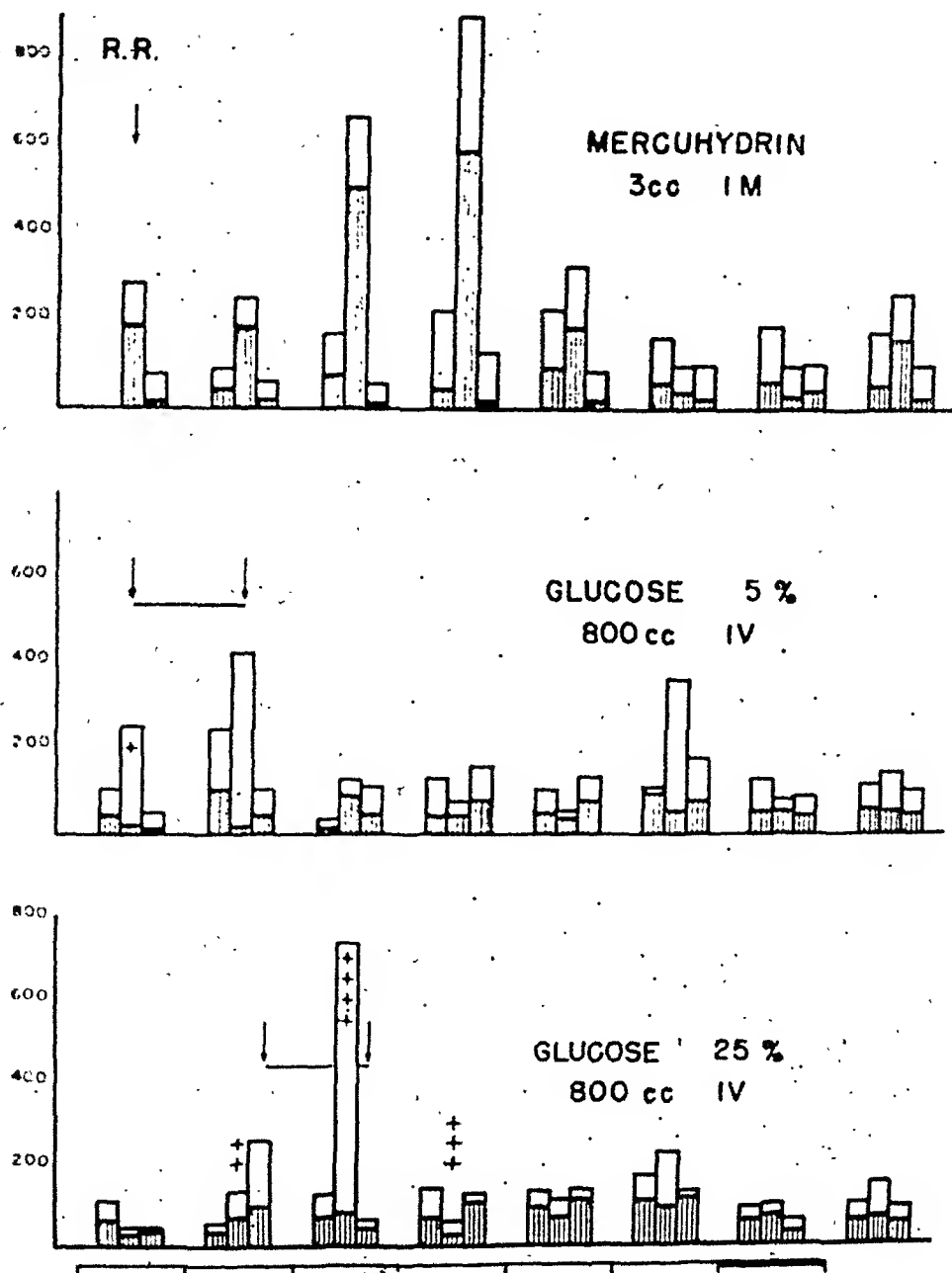


Fig. 5.—Graphic representation of the excretion of urine and sodium for two-hour intervals during the day when 5 per cent or 25 per cent glucose (dextrose) was given intravenously. The arrows indicate the duration of the infusion, about two hours. The overnight specimens were pooled and the two-hour average output is plotted over the wide bar in the base line. The total output for the twenty-four hours is also plotted as a two-hour average. The Mercurhydrin is included for contrast. Each 3-column group represents the same two-hour interval in the day on three successive days. The plus signs indicate glycosuria.

The Effect of Mercurial Theophylline Compounds on Sodium Excretion.—When theophylline is added to the mercurial compound (Salyrgan-theophylline or Mereuhydin) an effect similar to that obtained with mercurials alone is observed. These data are recorded in Figs. 5 and 8. A considerable increase in urinary sodium excretion is obtained through the mechanism of increased sodium concentration and increased urinary volume.

The effect of Mereuhydin appears within an hour and increases over a period of seven to eight hours (Fig. 5). In this case the amount of sodium excreted in the fourth two-hour interval exceeded the total excretion of the preceding control day. On the basis of these observations it appears that the mercurial compounds are most effective in mobilizing sodium.

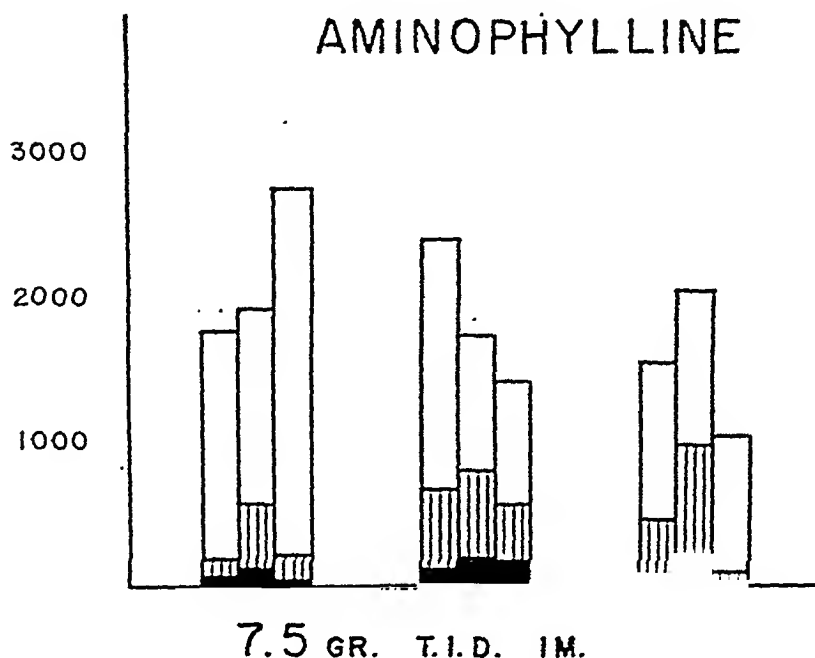


Fig. 6.—Graphic representation of the excretion of urine and sodium when aminophylline (7.5 grains t.i.d. = 1,500 mg.) was given intramuscularly.

The addition of theophylline to the mercurial agents does not increase their diuretic effect. It was noted that there was no vomiting in this series. Small non-nauseating doses of aminophylline were shown to be ineffective in mobilizing sodium. In all probability the lack of any additive effect obtained by this combination is due to the very small amount of the xanthine in the mercurial diuretics. (100 mg. to 200 mg.)

The Effect of Ammonium Chloride on Sodium Excretion.—Ammonium chloride has been the standard diuretic agent used in this clinic during the past years. It has been customary to give 8.0 Gm. daily in divided doses, and to continue it for four days. The effect of this regimen on mobilizing and excreting sodium and water was studied. In addition, some patients were given 12 and 16 Gm. of ammonium chloride daily, both orally and intravenously. The patients were on a standard diet containing 7.0 Gm. of sodium chloride a day. Eight grams of ammonium chloride caused a slight increase in sodium excretion, while 12.0 Gm. daily produced a significant increase in both urinary volume and sodium excretion per twenty-four hours. The sodium concentration, however,

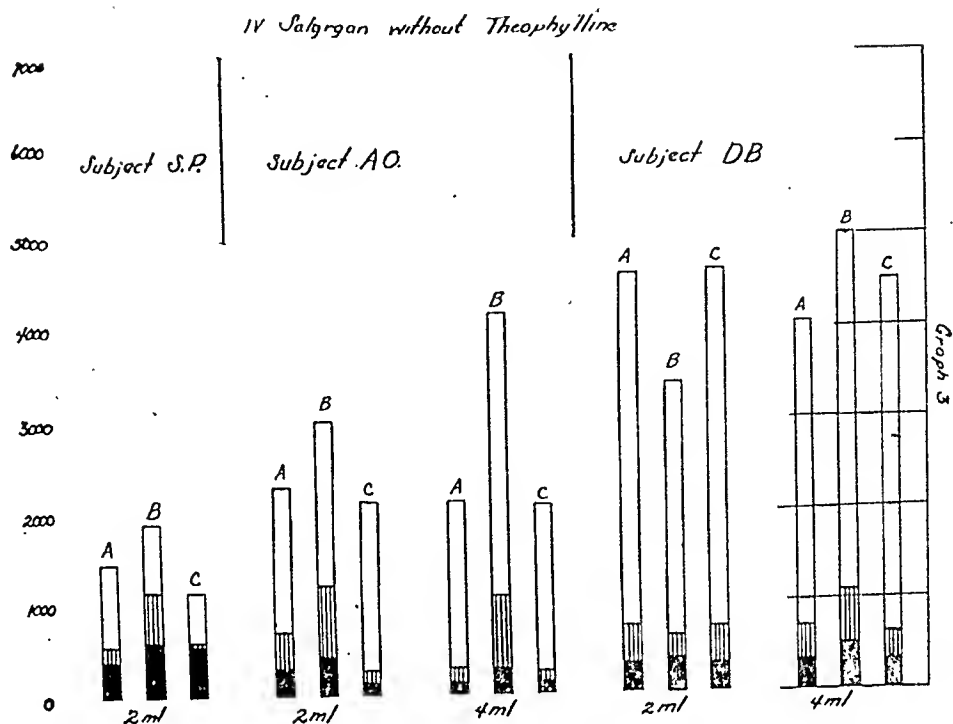


Fig. 7.—Graphic representation of the excretion of urine and sodium when salyrgan was administered in doses of 2 and 4 c.c. (ml).

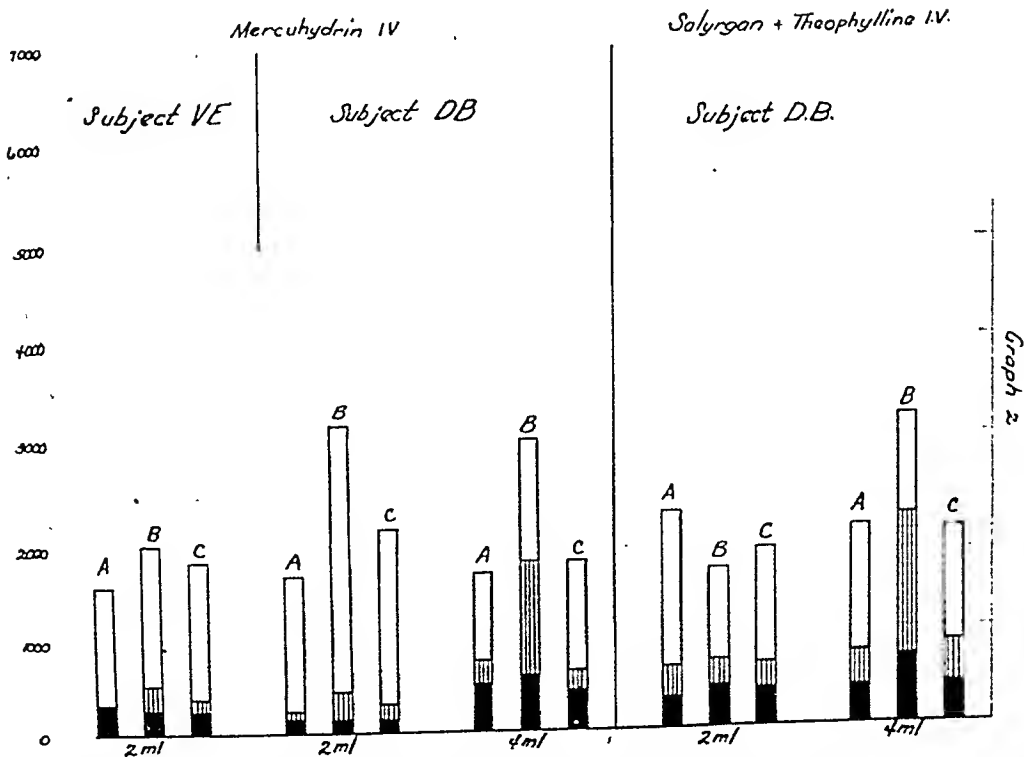


Fig. 8.—Graphic representation of the excretion of urine and sodium when mercurhydrin or salyrgan-theophylline was given in doses of 2 and 4 c.c. (ml) (mercurial 200-400 mg. with theophylline 100-200 mg.).

was not increased; the increased sodium output was due to increased urinary volume. Sixteen grams of ammonium chloride had an inconsistent effect probably because of interfering vomiting. Apparently there is no increase in sodium excretion over that due to the 12 Gm. dose, suggesting that that amount represents an optimal dose. It became apparent that the maximal effect was obtained within twenty-four to forty-eight hours and that continued treatment had no

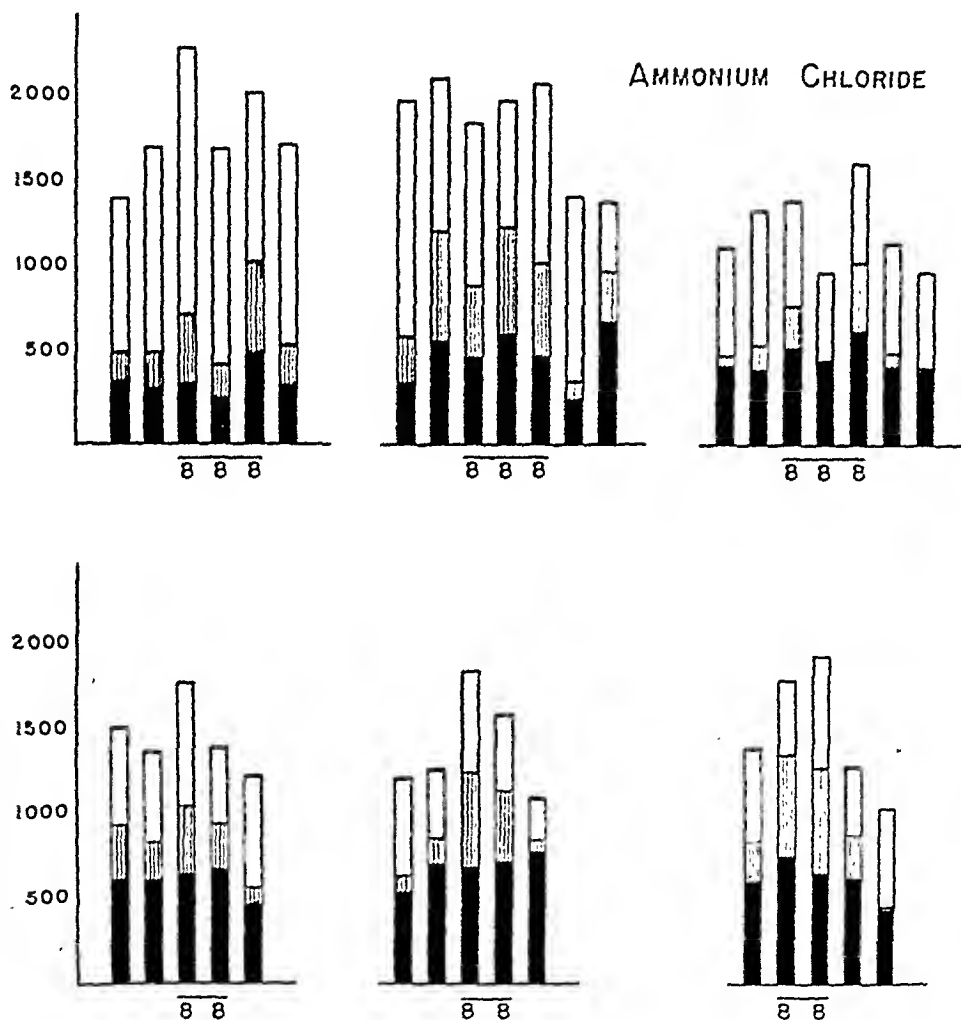


Fig. 9.—Graphic representation of the excretion of urine and sodium when 8 Gm. of ammonium chloride and given for three days (upper row of three patients) and given for two days (lower row).

effect on urinary sodium excretion or urinary volume. A decrease in sodium excretion occurred in some patients during the continued administration of ammonium chloride (Figs. 9 and 10).

When the dietary sodium was decreased to 2.0 Gm. per twenty-four hours, ammonium chloride had no effect on urinary sodium output. Apparently there must be a fair supply of available sodium for its increased excretion to be obtained with ammonium chloride.

It has been suggested that the ammonium chloride produces its effect through the following mechanisms: The ammonium ion is combined with carbon dioxide in the liver to produce urea. The urea is a neutral substance

and is excreted as such. The negative chloride ions produce a state of acidosis which is reduced by a reaction of the excess ehloride ions with the sodium bicarbonate buffer to form sodium ehloride and carbon dioxide. Sodium ehloride is excreted in the urine and carries with it an increased volume of water; the carbon dioxide is eliminated through the lungs and further reduces the acidosis.

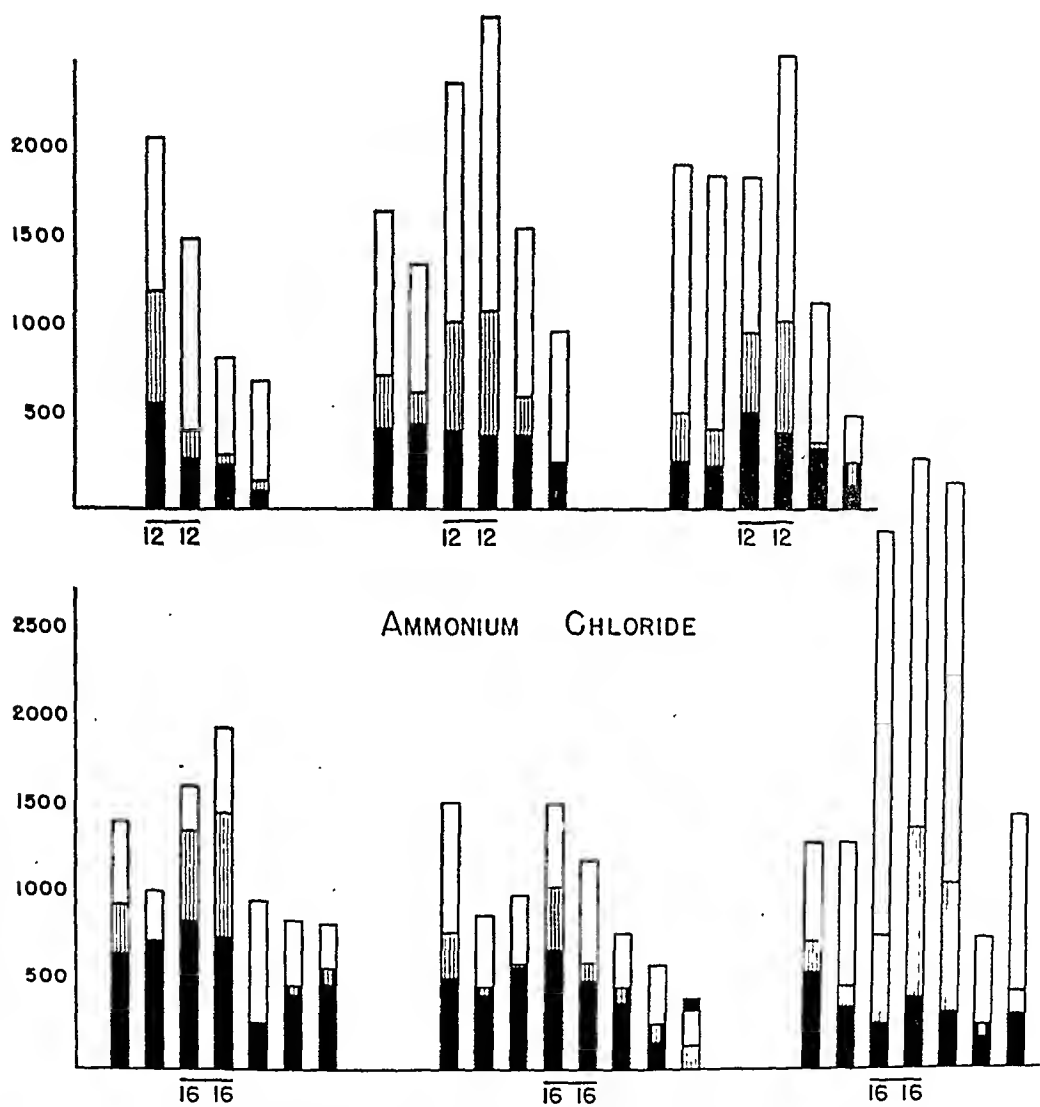


Fig. 10.—Graphic representation of the excretion of urine and sodium when 12 or 16 Gm. of ammonium chloride was given for two days.

The validity of this theory was tested by measuring urinary sodium, ehloride, ammonia, urine volume, and blood carbon dioxide combining power. The results are tabulated in Fig: 11. This concept seems to be basically eorrect for there was an increased urinary sodium and urea associated with the increased urinary volume. There was also an increase in ehloride more than could be accounted for by the increased urinary sodium. The absence of an increase in urinary ammonia indicates that little if any ammonium ehloride is excreted. The excess ehlorides found in the urine were in combination with some unde-termined cation. In these patients the increase in sodium excretion was asso-iated with a drop in carbon dioxide combining power, which indicates a loss of buffer sodium salts.

In a prior study observations on weight loss and changes in blood carbon dioxide combining power were recorded during the intravenous injection of ammonium chloride.

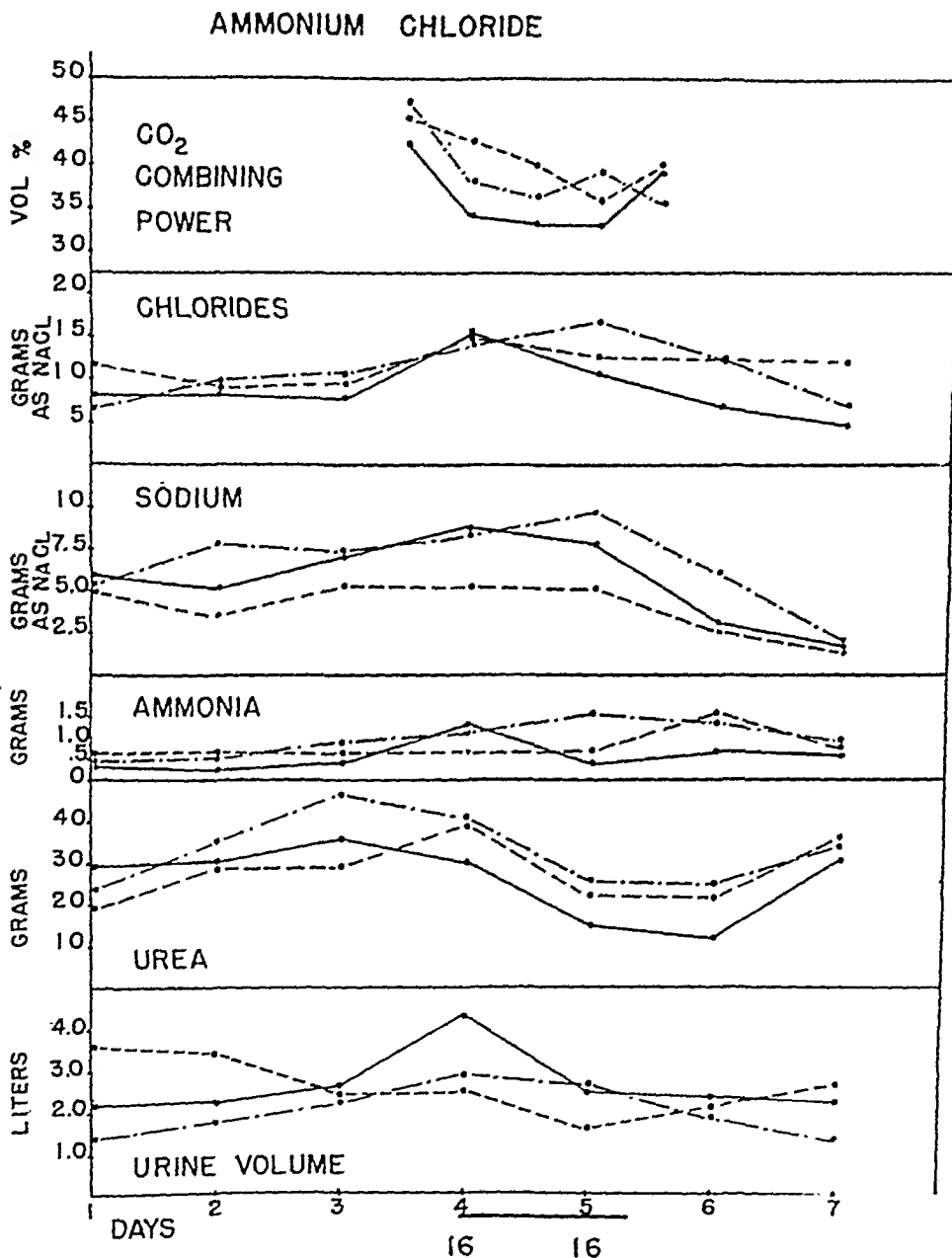


Fig. 11.—Variations in urinary constituents and blood carbon dioxide combining power when 16 Gm. of ammonium chloride was given to three patients.

Ammonium chloride was prepared as chemically pure crystals and autoclaved in ampules. It was determined that from 0.5 to 1 per cent ammonium chloride in 5 per cent dextrose would not produce hemolysis in vitro and was a satisfactory solution for intravenous injection. When 10 to 15 Gm. of ammonium chloride were injected into patients, vomiting occasionally occurred. Rapid injection seemed to favor vomiting. This suggests that the vomiting associated with ammonium chloride administration may be central in origin.

It was observed that effective mobilization of edema occurred over a short period of time and was associated with a considerable decrease in the blood carbon dioxide combining power. (Fig. 12.) Prompt weight loss can be induced by the intravenous injection of ammonium chloride and the resulting acidosis.

It thus appears that ammonium chloride administration can increase urinary sodium excretion, that this increase is of short duration, and may not be maintained even with the continued administration of the drug. The increase in sodium excretion is effected by an increase in urinary volume rather than by increased sodium concentration. Twelve grams of ammonium chloride seems to be a satisfactory daily dose.

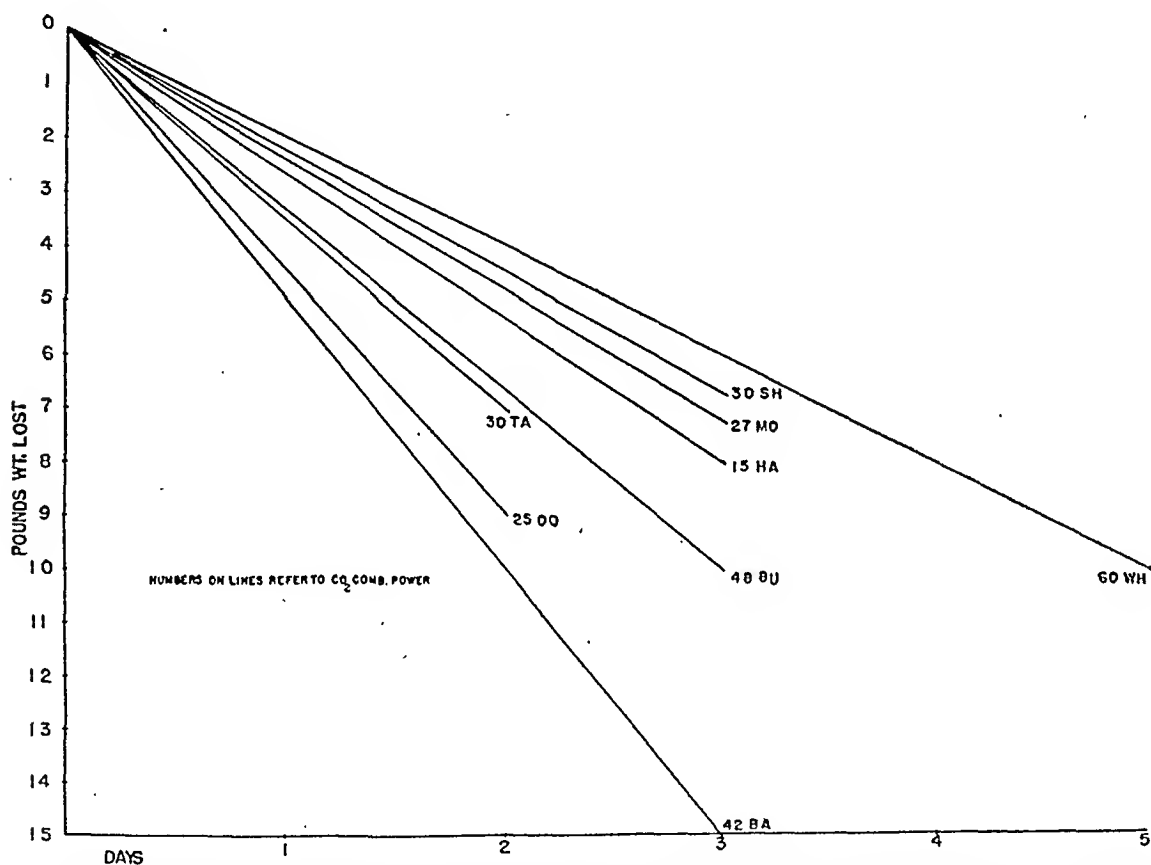


Fig. 12.—Graph showing weight loss in eight toxemic patients given 10 to 15 Gm. per day of ammonium chloride intravenously in 5 per cent dextrose. The figures represent carbon dioxide combining power and the patients' initials.

The Effect of Urea on Sodium Excretion.—It has been suggested that urea is a diuretic agent that operates by increasing urinary volume. In order to determine the effect of urea, patients were given 60 Gm. of urea daily. The data from these studies are recorded in Fig. 13. There is a questionable transitory increase in urinary volume, which may be due to the considerable volume of fluid necessary to ingest the urea. There was no increase in urinary sodium and no alteration in sodium concentration in the urine.

Sodium and Water Excretion in Toxemic Pregnancies.—It is apparent from the above data that certain agents are more effective in the mobilization and excretion of sodium than are others. Since these studies were carried out on

normal pregnant patients it was of interest to determine whether a similar mechanism was operative in patients with toxemia of late pregnancy. Three patients with moderately severe toxemia were studied with regard to both sodium and urinary excretion. They were placed on the usual routine of low sodium diet, liberal fluids by mouth, 8.0 Gm. of ammonium chloride daily, and bed rest. After stabilization on this schedule, they were given intravenous dextrose; there was a slight increase in urinary volume but no increase in a twenty-four-hour sodium output. Two cubic centimeters of Mercurhydrin were then given and it produced both a marked diuretic and sodium excretion effect. This suggests that toxemic patients respond similarly to normal pregnant women as regards the dextrose and mercurial diuretics.

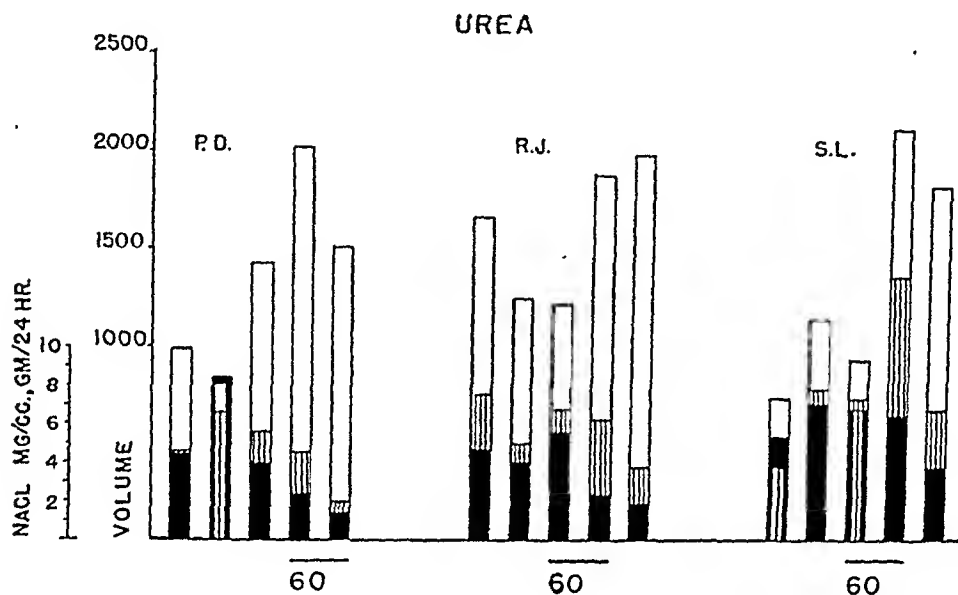


Fig. 13.—Graphic representation of the excretion of urine and sodium for three nonpregnant subjects receiving 60 Gm. of urea on two successive days.

The patients reported under the section on intravenous ammonium chloride (Fig. 12) all had toxemia and showed a very satisfactory weight loss indirectly indicating loss of water and sodium. Three eclamptic patients who had progressed to the point of marked oliguria (10 c.c. per hour or less) or complete anuria were given varying concentrations of glucose by vein without effect. Seven and one-half grains of aminophylline were given intramuscularly and in two of the three patients urinary flow was established within a few hours. These urines contained high concentrations of sodium. This suggests that anuric and oliguric patients may respond to aminophylline in a similar manner to normal pregnant women.

Sufficient studies have not been made on toxemic women to indicate the effectiveness of these agents in the clinical management of the disease. These notations are included because they suggest that the mechanism of sodium excretion is of a similar nature in normal and toxemic pregnancies.

An attempt was made to test the suggestions that morphine might have an antidiuretic effect. Twenty patients were given variable amounts of 5 per cent dextrose intravenously at a constant rate each day. On alternate days they were given 10 to 15 mg. of morphine at the onset of the infusion. Many but not all of these patients showed a sodium and water retention for three or four

hours. If these observations are confirmed, they suggest that the large doses of morphine commonly used in the control of eclampsia may contribute to an oliguria or anuria.

Discussion

From the experimental data, it becomes apparent that sodium excretion is a complex process and that a variety of factors modify its mobilization. From the standpoint of clinical management of toxemic patients, no evidence is presented as to the relative value of increasing urinary volume or urinary sodium excretion. These studies do not offer any evidence on the basic abnormality productive of edema, namely, whether it is a disorder of sodium or water metabolism. The effect of diuretic agents on twenty-four-hour urinary volume and sodium excretion is relatively transitory. Except in the case of ammonium chloride, no attempt has been made to introduce these agents continuously. As far as the mercurials were concerned, this was avoided both because of concern about potential renal damage to the women and because of statements in the literature that the effect would last for several days. The data obtained in these experiments suggest that the effect on sodium excretion is relatively transitory, lasting about twenty-four hours. In the case of ammonium chloride even the continued administration of the drug is not attended by maintenance of increased urine or sodium excretion.

In practically every case following excessive sodium mobilization, there was a transitory (probably compensatory) retention of sodium apparently to permit a restoration of sodium balance. Sodium retention was especially marked the day after the use of mercurials or large doses of aminophylline. It is interesting to note that with hypertonic glucose there is a transitory increase in urine volume apparent only when hourly fractionated studies were run. However, even during the diuretic phase the amount of fluid eliminated is not as great as that injected and then a period of oliguria and decreased sodium excretion follows within two hours.

It became apparent that the so-called diuretic agents have been very loosely defined. When one introduces 1,000 c.c. of fluid into the blood stream and recovers 800 c.c. of urine, it becomes a question as to whether or not the fluid represents a diuretic. Hourly urine collections show an apparent increase in urinary volume over and above the control period. If this increase in urine output is less than the normal excretion plus the increment introduced by vein, it becomes a matter of opinion as to whether the increase in urine is a straight filtration phenomenon produced by the fluid introduced, or whether it represents a diuretic effect. Since the total output is less than the total intake (whether measured on an hourly or on a twenty-four-hour basis) these studies suggest that hypertonic solutions of crystalloids introduced into the blood stream are ineffective as diuretics. However, by contrast, the introduction of 3 to 4 c.c. of a mercurial diuretic will cause a marked increase in urinary volume in which the fluid volume of the injected material becomes negligible. It would seem that

the latter type of agent might be rightfully called a diuretic. This group includes the mercurial and xanthine compounds. It is of interest in this connection to consider the effect of intramuscular aminophylline in large doses. Despite a decreased intake of fluid and sodium induced by vomiting, there may be increase in urinary volume. Thus it becomes apparent that aminophylline is a diuretic agent in that it can mobilize and excrete fluid and sodium even in the face of decreased intake.

It is of interest to note that some preparations which are popular as diuretics such as urea and dextrose were shown to be ineffective in that they did not increase urine output.

There seems to be a slight increase in urine volume and sodium excretion induced by adequate amounts of ammonium chloride. It is of interest to note that this effect of ammonium chloride is almost entirely eliminated by the sharp reduction in dietary sodium. Explanation of this phenomenon is not apparent. It would appear that the effect of the shift in the acid base balance, which necessitates the mobilization of sodium and other buffer salts, takes place only in the presence of available sodium. Moreover, the continued administration of ammonium chloride over the second and third day, after an increased sodium excretion has been obtained, is relatively ineffective.

The increase in urinary volume associated with ammonium chloride administration is difficult to evaluate. The patients who received the 12 and 16 grams of ammonium chloride became thirsty and ingested a larger volume of water. The increase of urinary output, therefore, may simply represent a function of the increased ingestion of fluid rather than any direct diuretic effect of ammonium chloride.

When one studies the effects of these diuretic agents on sodium excretion, their action tends to fall into three general categories. In the first place increased urinary sodium output can be induced in patients by giving fluid by vein. While this effect is slight, it is apparent when hypotonic solutions are given in a relatively short period of time. The increased urinary sodium excretion is obtained with a decreased sodium concentration in an increased output. This type of effect we have called a "wash out" mechanism. It appears that the increased urinary sodium is obtained by the direct effect of an augmented urinary volume produced by the increased fluid intake.

A second mechanism of increased sodium excretion is produced by a change in acid base balance. Ammonium chloride is the best example of this type. An increase in urinary sodium can be obtained if one produces a rather rapid and sudden shift toward the acid side. Apparently this change mobilizes sodium to compensate for a relative acidosis, and thus an increased amount of sodium is excreted by the kidneys.* This increased sodium excretion is brought about by

*While most authorities suggest that the diuretic effect of aminophylline is due to a change in glomerular filtration it is of interest to note that the clinical picture of nausea, dizziness, vomiting, and thirst which are apparent with ammonium chloride medication, is likewise apparent in the large effective doses of aminophylline.

an increase in urinary volume but without change in sodium concentration. This is in contrast to the decreased sodium concentration found in patients described under the "wash-out" process discussed above.

The third mechanism by which sodium excretion may be increased is through some change in renal function. Mercurial and xanthine diuretics produce this type of effect. They cause a moderate increase in urinary volume and the most marked increase in total urinary sodium of any of the agents studied. This effect can be obtained with either the mercurials or aminophylline but, from the pharmacological point of view, there seems to be little advantage in combining the two as in the commercial compounds. Because of the small amounts of aminophylline in the pharmaceutical preparations, it is impossible to judge the additive effect produced by the combination. It would be of interest to learn whether an increased amount of aminophylline together with a mercurial diuretic would cause an augmented effect.

While the studies which are available on toxemic patients are too few to be of any clinical value, it is of interest that apparently the toxemic patient handles water and sodium in a manner similar to the normal pregnant woman and will respond in a similar fashion to diuretic agents. The evidence available suggests that the mercurials and xanthines are worthy of clinical trial in the management of toxemic patients.

The clinical management of toxemic patients generally includes a liberal use of sedatives, such as morphine. If the observations of the antidiuretic effect of morphine are confirmed, its use in patients with oliguria may need to be restricted.

As yet there is no good explanation why the toxemic patients who excrete large volumes of urine and are losing weight have a better prognosis than those patients who do not respond. Nevertheless, there is general clinical agreement that such is the case. It would appear, therefore, that, on the basis of these experimental observations, toxemic patients might be improved by the clinical trial of some of these preparations. In all probability, the edema is not the cause of toxemia of pregnancy but is merely a symptom of an underlying biochemical derangement which has not yet been identified.

Conclusions

1. Diuretic agents vary in their ability to increase the excretion of water and/or sodium.
2. Diuretic agents increase sodium excretion by three mechanisms: (a) by a "wash-out" process induced by increased fluids given intravenously; (b) by the production of an acidosis; (c) by a change in renal function which increases the concentration of sodium in the urine.
3. Hypertonic dextrose solutions do not increase sodium or water excretion.
4. Induced increases in sodium excretion are transitory (twenty-four to forty-eight hours).
5. Apparently toxemic and normal pregnant women respond similarly to diuretic agents.

We are indebted to Donna MacLachlan, Betty Jean Harpley, and Erlene Peterson for the dietary management and for the sodium determinations on the patients used in this study.

Addendum

Since submitting this manuscript for publication, we have given hypertonic dextrose intravenously at a more rapid rate in four instances. Normal women were given 800 c.c. of 25 per cent dextrose at a rate of 0.25 c.c. per kg. (approximately 16 c.c.) per minute. During the forty-five to fifty minutes of the infusion, the output of urine increased when the blood sugar concentration exceeded 500 mg. per cent and the urine sugar concentration was over 1 per cent. However, the increase in urine flow over that of the control interval was less than 16 c.c. per minute so that not all of the infused fluid was recovered. In only one fifteen-minute interval, in one patient, did the increase in urine flow equal or exceed the 16 c.c. per minute increment which was given as 25 per cent dextrose. In two instances the urine output decreased during the last fifteen minutes of the infusion. Immediately after the discontinuance of the intravenous dextrose, the urine flow diminished rapidly as the blood sugar levels dropped.

The abrupt decrease in urine flow after the administration of hypertonic solution was discontinued, and its decrease during the infusion in two instances, suggested that the increased osmotic pressure of the blood may have caused the liberation of antidiuretic hormone from the posterior pituitary. This response of the neurohypophysis would tend to defeat the purpose of the hypertonic intravenous fluid.^{4, 5, 6} Even though the urine output was increased during the rapid infusion of dextrose, in our experience, this increment of urine was not apparent in a total twenty-four-hour urine volume and was less than the amount of extra fluid administered.

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Discussion

DR. FRANK E. WHITACRE, Memphis, Tenn.—Drs. Brown and Bradbury have brought out so many factors in this timely report that any one of them could be the subject of debate among the physiologists, pathologists, and clinicians. In reviewing this extensive piece of work, water balance is of special interest.

Dextrose, from this report, is no better as a diuretic than water. It would be helpful to know more accurately the speed of administration of hypertonic dextrose solution, as it is well known that this has considerable effect upon the volume of urine returned, and, to expect a diuretic effect, the renal threshold must be exceeded. Some of the water is retained with glucose as the glucose is rapidly absorbed from the blood. Any procedure which attempts to increase sodium excretion will be followed by a period of sodium retention until the balance is restored. Sodium and water are presumably retained in the body by some extra renal mechanism. One can reduce water and sodium temporarily, but after the diuretic procedure is stopped, both are retained as before. Sodium and water retained in edema fluid are inaccessible to the kidney unless some diuretic agent is used. Water excretion reflects primary reciprocal changes in tubular reabsorption of water. Daily variations in water excretion are believed to be due to changes in facultative water reabsorption through the antidiuretic

hormone mechanism. It is possible that this mechanism is involved in the disturbances of our toxemic patients. The amount of sodium and chloride reabsorbed varies inversely with the A. D. H. concentration, but the amount of water reabsorbed varies directly.

The combination of ammonium chloride and dextrose seems to be innocuous treatment and caused considerable weight loss through the excretion of water and salt. However, if used for very long, acidosis could result due to depletion of alkali reserve.

The effect of mercurial diuretics is that they block the tubular absorption of sodium and chloride. They have been considered to be ideal diuretics and widely used, and the suggestion of the authors that they be given a try in toxemic patients must be carefully considered. There is evidence that the mercurials can cause necrosis of the convoluted tubules leading to irreparable damage. Sprunt has reported that in 741 autopsies, nine had received mercurial diuretics and of these, three showed necrosis of the tubular epithelium. He could not correlate the amount given with the extent of the renal damage (*Arch. Int. Med.* 46: 494, Sept. 1930). It seems reasonable to conclude that where contraindications, such as fever, tuberculosis, or chronic nephritis are present or, if there is evidence of kidney damage, the mercurial diuretics should not be used.

The effects of the various diuretic agents mentioned should not be left without emphasizing another factor. Generalized angiospasm in the toxemic patient could be expected to reduce renal blood flow, and the effect of diuretic agents is enhanced by relieving by various commonly applied means the spasticity of the arterioles.

It is a good thing for someone to bring into question our established ideas on what a diuretic really is, and it is questionable that a substance can be considered as a diuretic when the amount of fluid given to the patient so far exceeds the amount returned in the urine.

DR. LESTER ODELL, Chicago.—During the past six months at the Chicago Lying-in Hospital the effect of the various diuretics has been reinvestigated. Our efforts have been directed toward urine sodium and the volume of urine excreted. Employing the diuretic agents recommended by Dr. Brown, we found more sodium excreted and a greater urinary volume following hypertonic glucose. We feel that the urinary volume is the best single prognostic guide we have in eclampsia. We have advocated the use of intravenous hypertonic glucose in maintaining an adequate urinary volume, and recommend 1,000 ml. of 20 per cent glucose every eight hours. If such concentrations are unsuccessful, use 750 ml. of 30 per cent or 400 ml. of 50 per cent glucose solutions. Hypertonic glucose is the best thing available at present for maintaining the adequate urine volume so necessary for recovery of the eclamptic patient.

I would like to ask Dr. Brown two questions: First, how many severe toxemias of pregnancy have been treated by mercurial diuretics alone? And by the term "diuretic" I mean to include hypertonic glucose solutions. Secondly, in using mercurial diuretics clinically, how can one be sure that no renal disease exists? In short, how will one differentiate between severe preeclampsia and nephritis prior to the use of mercury?

DR. BROWN (Closing).—We wish to point out that this report was designed to make available basic information about the action of these diuretic agents in excreting sodium. We have presented no evidence that sodium or water retention has necessarily anything to do with the outcome of toxemia of pregnancy. It is generally agreed that if an increased urinary volume is obtained, these patients are improved. These observations offer mechanisms by which increased urinary sodium and volume can be accomplished. It is yet to be proved that these changes have a beneficial clinical effect.

The question of what constitutes a diuretic has to be considered. According to our interpretation, if one administers 1,000 c.c. of solution to a patient and recovers only 500 to 800 c.c. in the urine, that agent is not a diuretic. I do not disagree that the patients at the Chicago Lying-In Hospital are improved, but I do question that intravenous hypertonic glucose solution is a diuretic agent.

In answer to Dr. Whitacre's question, I would like to show three slides. The first slide demonstrates the similar effect produced by giving 6,000 c.c. of water in three hours and in

twenty-four hours (Fig. 2). The second slide compares the effect of intravenous glucose (isotonic and hypertonic) given in two hours (Fig. 5) and over six hours (Fig. 3). The rate of administration in these experiments had no apparent effect on the twenty-four-hour urinary volume or sodium output.

From these studies it is apparent that sodium and water excretion can be manipulated independently of each other. Increased urine volume may be obtained with both high and low concentration of sodium. Likewise, the amount of sodium in the urine can be increased with minimal increase in urine volumes.

In presenting this material, we hope others will be encouraged to try these agents in the clinical management of toxemia so that we may come to learn their true value. We now have a method for studying both sodium and water excretion independently of each other.

MESONEPHRIC REMNANTS IN THE CERVIX*

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(From the Department of Obstetrics and Gynecology, Northwestern University Medical School)

IT IS well known that certain portions of the mesonephros may persist near the ovary and in the broad ligament and the vagina of the adult human female. That fetal remnants of mesonephric origin may persist in the uterine cervix is less commonly realized. From time to time reports have appeared in the European literature commenting on the development of tumors arising from mesonephric residues in the cervix. Meyer¹⁻³ has presented factual data establishing the embryonic source of such neoplasms as being from the cervical portion of the mesonephric duct.

With the exception of Wolfe's case reports several years ago,⁴ the American literature has contained no reference to this unique and unusual problem. It should be a matter of interest shared in common by the clinician, the gynecologic histopathologist, and the embryologist. This is particularly true when it is realized that mesonephric remnants in the cervix may cause confusion in the histologic study of surgically excised tissues and that they may give rise to bizarre tumors which can be either benign or malignant. Because of the paucity and the relative inaccessibility of available information on the subject, it has seemed worth while to make this presentation an attempt to portray in definitive fashion the embryology, the histology, and the microscopic pathology of mesonephric remnants in the uterine cervix. In order to accomplish this the literature has been reviewed, serially sectioned tissues have been studied, and sections from 1,192 surgically excised cervixes in the gynecologic laboratory at Northwestern University Medical School (comprising tissues from Passavant Memorial and Wesley Memorial Hospitals) have been examined.

In the development of the female urogenital system it will be recalled that the first primitive organ is the pronephros and that as a result of fusion of the pronephric tubules a pair of collecting ducts develop. After the degeneration of the pronephros the two excretory ducts persist as the mesonephric (wolffian) ducts into which the mesonephric tubules empty (Fig. 1). These ducts extend caudally along each side of the celomic cavity to empty into the ventrolateral portions of the cloaca. The paired paramesonephric (müllerian) ducts extend first lateral and then medial to the mesonephric ducts. As the mesonephric and paramesonephric ducts increase in size, a fold of peritoneum (the urogenital fold) grows about them. The caudal portions of these two lateral urogenital folds fuse transversely in the lower abdomen to form a medially placed genital cord. In the center of this genital cord are the two paramesonephric ducts

*Read by invitation, before the Central Association of Obstetricians and Gynecologists, Oct. 25, 1947, Louisville, Ky.

(müllerian) which later fuse to form the uterovaginal canal. Somewhat lateral to the paramesonephric ducts but still within the genital cord are the paired mesonephric ducts.

From the 4 to the 55 mm. stage of embryonic development the mesonephric ducts empty into the cloaca and later the urogenital sinus. During this period they lie in the genital cord parallel and lateral to the paramesonephric ducts and are intact throughout their lengths (Fig. 2). Shortly after the 55 mm. stage, however, the openings in the urogenital sinus close and degeneration of the mesonephric ducts begins (Fig. 3). This degeneration continues throughout the remainder of embryonic life and in most individuals only a few vestiges of the mesonephric tissues persist: in the adult degenerated portions may be found near the ovary, in the mesosalpinx, and in the broad ligament. Occasionally persistent portions of the mesonephric ducts become dilated in the anterolateral or lateral vaginal walls to form the familiar Gartner's duct cysts.

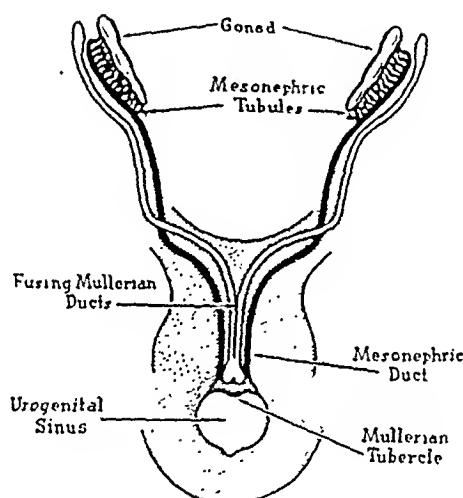


Fig. 1.—Diagram of the urogenital system at an early stage in fetal development. The mesonephric ducts extend caudally along each side of the fusing paramesonephric ducts within the genital cord.

While the sequence of events in the development and degeneration of the mesonephric tissues as just described applies to the majority of individuals, Meyer has demonstrated that certain interesting exceptions may occur. Meyer⁵ has shown that an ampullar dilated portion of the mesonephric duct is frequently observed as a rather wide circular enlargement of the duct lumen in the fetus as early as the second month. In older embryos the mesonephric duct is occasionally found as a narrow cylindrical tube penetrating from the parametrium into the middle of the lateral uterine wall. From this point of entrance the duct proceeds in a downward direction in the uterine wall (Fig. 4). As it enters the lowermost corpus and cervix the narrow cylindrical lumen dilates to form a distended ampulla located in the middle muscle layers of the lateral cervical walls. At the end of the fifth month of fetal life the ampulla forms a clefthlike cavity which has, in cross section, slight bends and curves and the beginnings of a few rather large diverticula (Fig. 5).

When the mesonephric duct persists in the cervix (in approximately 20 per cent of the fetuses Meyer⁶ examined), it reaches its full development at the seventh or eighth month of fetal life. At this time the ampulla lies chiefly in the lower part of the supravaginal portion of the cervix and in the upper portion

of the portio vaginalis. The dilated ampulla extends downward from the upper cervix as an elongated dorsoventral slit lying in the middle muscle layers of the lateral cervical walls. From the portio vaginalis the duct turns and runs laterally in a diagonal upward direction until it passes over into the vagina.

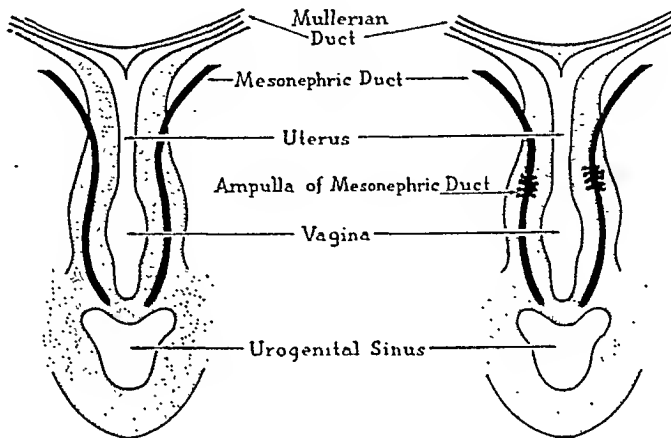


Fig. 2.—Diagram. Prior to their degeneration the mesonephric ducts extend along each side of the uterovaginal canal (which was formed by the fusion of the paramesonephric ducts, A. Mesonephric ampullae tubular diverticula develop in some (20 per cent according to Meyer) fetal uteri, B.

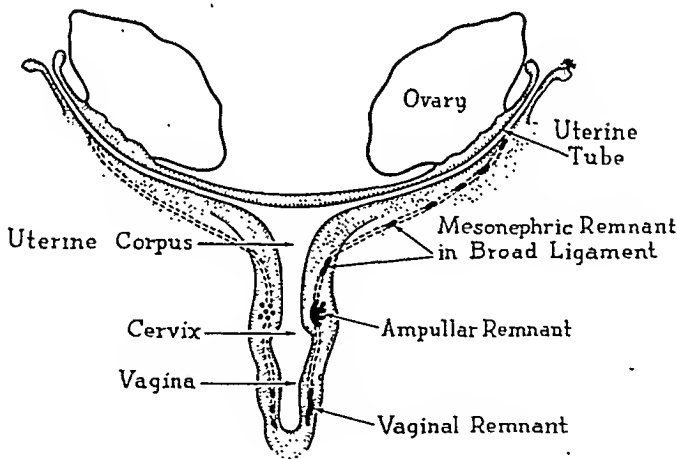


Fig. 3.—Diagram. Degeneration of the mesonephric duct begins during the later stages of fetal development. This degeneration may be complete or remnants may be left in the vaginal wall, the cervix, the uterine wall, or the broad ligament or near the ovary.

At the point where the ampulla turns laterally in the cervix it sends more or less deep branches into the substance of the cervix. These branches may form extensive coiled or snarled twisted canaliculi or tubules which extend into the anterior and posterior portions of the cervix. After the duct passes over into the vagina it again becomes narrower and assumes a cylindrical tubular form as it extends downward along the anterolateral vaginal wall to terminate near the hymen.

In the fetus a muscular tunie lies about the mesonephric duct cephalad to the ampulla (Fig. 6). This tunie consists of a broad inner longitudinal and a

thin outer circular layer. Along the course of the dilated ampulla the muscular tunic becomes relatively indistinct. In the same fashion a stroma of spindlelike cells is found about the duct above the ampulla (Fig. 6, A); there is little or no stroma about the canaliculi which branch off into the lower cervix.

In studying serial sections of fetal uteri stained with a trichrome stain (Milligan) it was noted that the stromal and muscular constituents of the mesonephric duct tend to persist after degeneration of the epithelial elements. As a result of this observation it was possible to follow the degenerating mesonephric duct in the uterine wall for some distance above the ampulla.

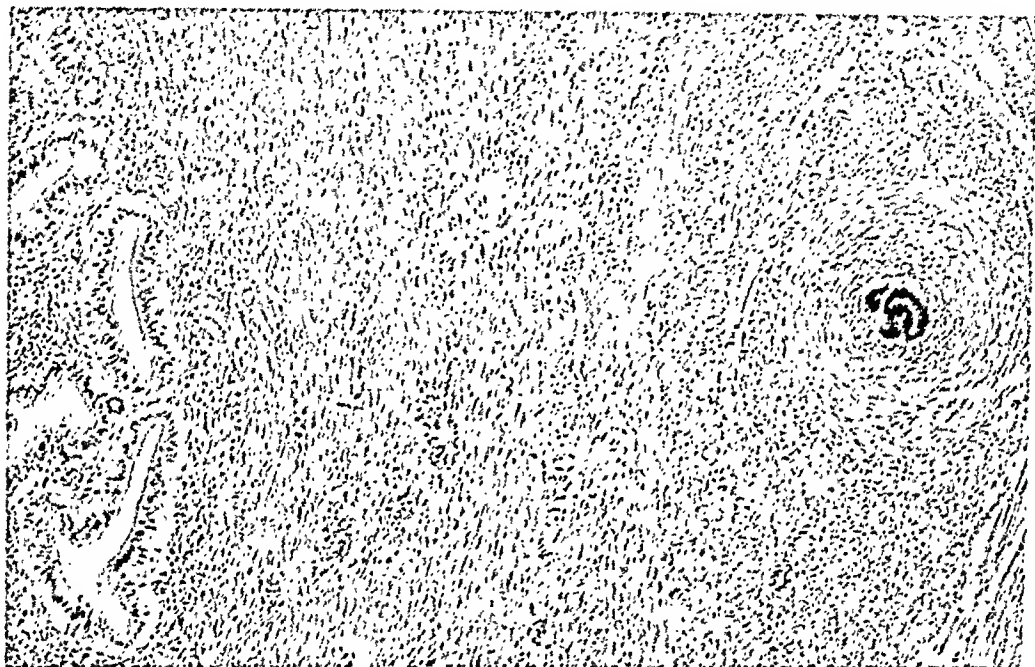


Fig. 4.—In the older embryo (7 months) the middle portion of the mesonephric duct may persist in the uterine wall. In this photomicrograph the mesonephric duct above the ampulla is seen as a curved canal lined by columnar epithelium and surrounded by a stroma of spindle-like cells. It has a distinct muscular tunic. The cervical glands are on the left.

The epithelium lining the duct cephalad to the ampulla consists of a single layer of cylindrical cells with oblong, almost rod-shaped nuclei (Fig. 6, B). The cells are highest in the dilated ampullar portion, while in the tubular ramifications the height of the epithelium is less and is proportional to the size of the tubular lumen. In the narrowest twisted tubules the epithelium is low cylindrical or cuboidal. In this cuboidal epithelium the nuclei tend to be spherical or ovoid. In the smallest tubules the cells of the epithelial lining often appear fused.

After reviewing the literature with the published case reports and studying the material available in this laboratory, it appears that remnants of mesonephric origin may be found in the adult cervix either as persistent fetal structures or as new growths arising from fetal residues. Those remnants which are not neoplastic may occur in several different forms. They may be seen as occasional small isolated tubules or canaliculi (Fig. 7, A) either in the middle portion of the cervical wall or near the mucosa in the region of the internal os. These isolated tubules are distinguished from the cervical glands (Fig. 7, B) by their

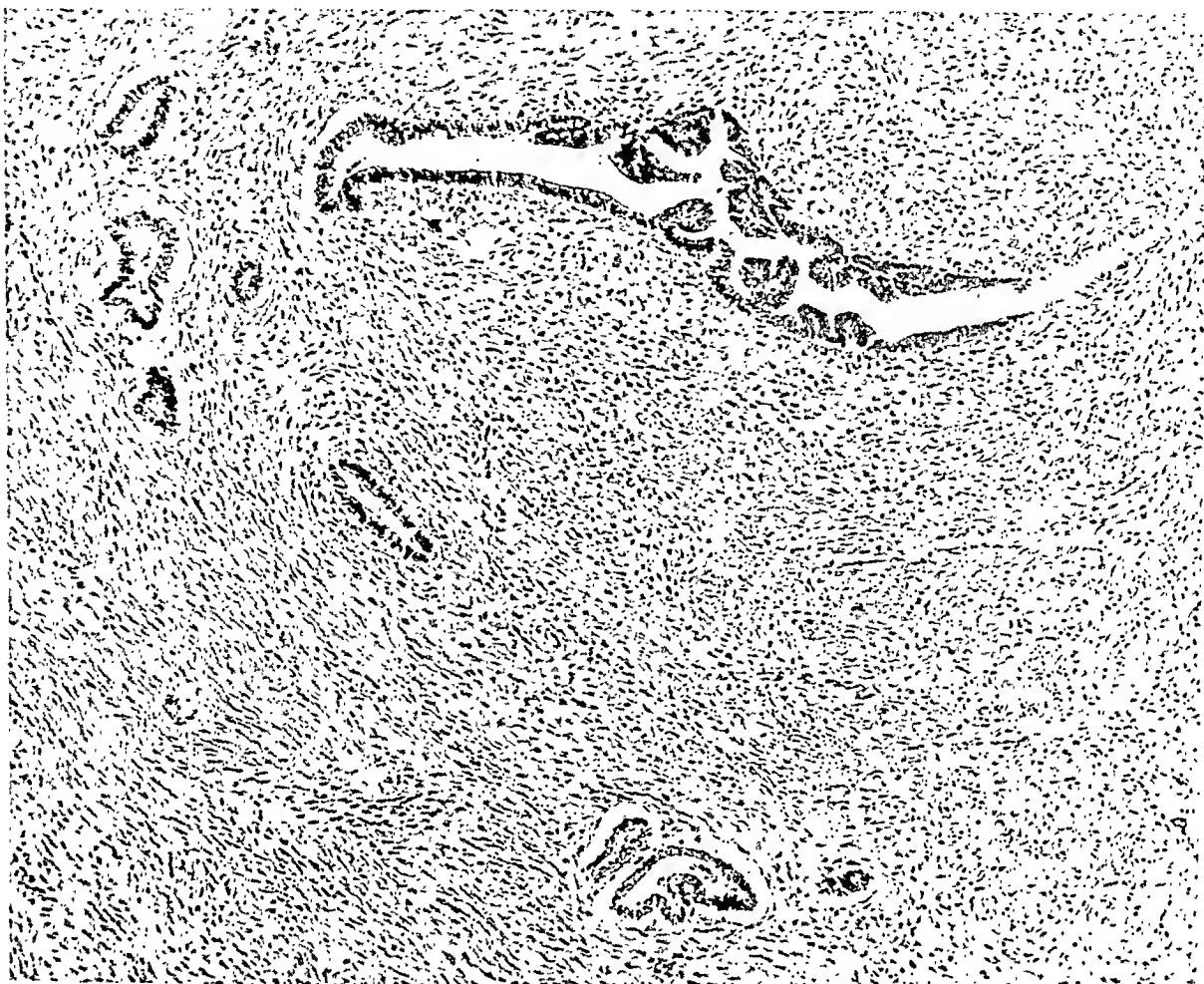
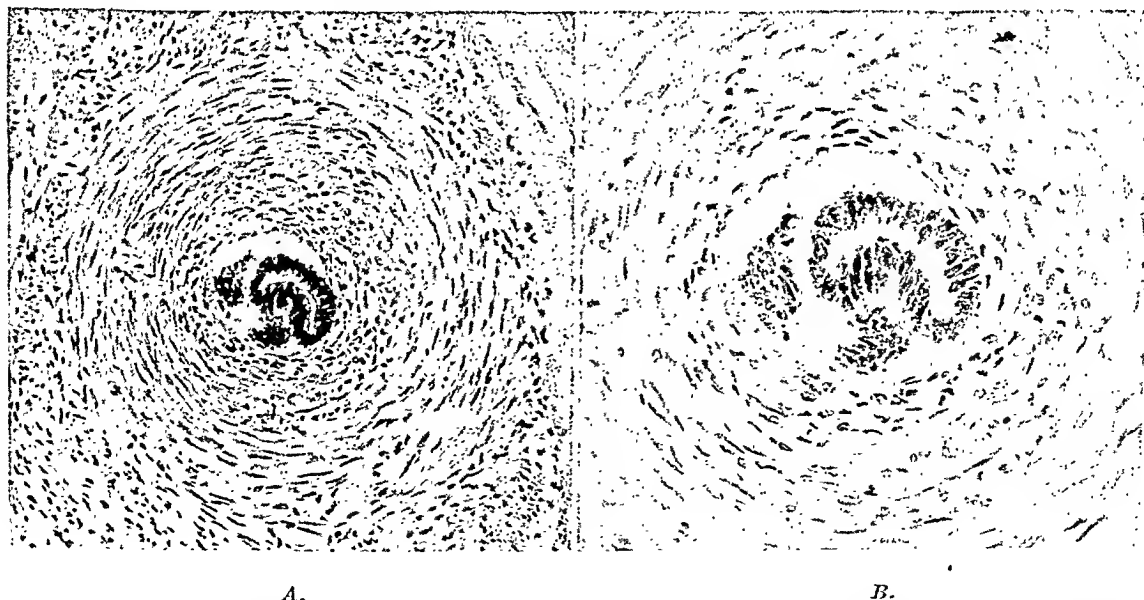


Fig. 5.—When the mesonephric duct persists in the cervix of older embryos it forms a cleftlike ampulla which has, in cross section, slight bends and curves and the beginnings of a few diverticula. Occasional tubules branch off from it. (Photomicrograph of a cross section through the cervix of a 7-month fetus).

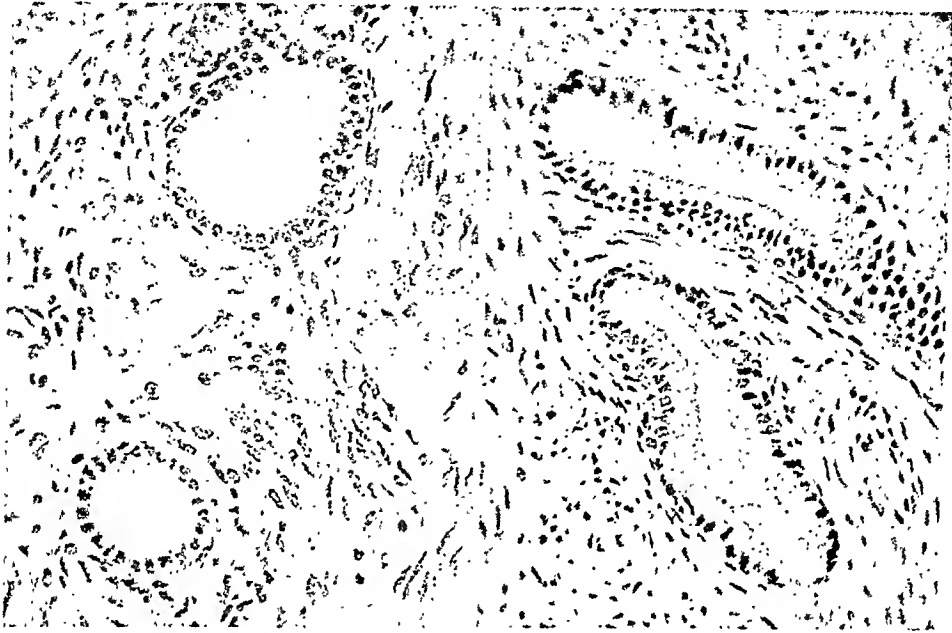


A.

B.

Fig. 6.—In the fetus the mesonephric duct cephalad to the ampulla has a distinct muscular coat, A. The epithelium lining the duct lumen is made up of columnar cells with oblong almost rod-shaped nuclei. A stroma of spindle-like cells lies between the epithelium and the muscular tunic, B.

distinctive low cuboidal epithelial lining and by their failure to take a mucicarmine stain. Often those scattered tubules lying in close proximity to the glands of the uterine isthmus so resemble the latter as to make differentiation between them difficult. More deeply within the cervical musculature closely approximated cystic dilations of several ampullar tubules with occasional smaller tubules about them may be found (Fig. 8). These have, again, a typical non-secretory low columnar epithelium. Differentiation between these ampullar tubules and cervical glands is less difficult than is the differentiation between isthmus glands and isolated mesonephric ampullar tubules near the mucosa.



A.

B.

Fig. 7.—Occasional isolated mesonephric ampullar tubules, *A*, may be found in the cervix. These tubules are distinguished from cervical glands, *B*, by their low cuboidal epithelium which is composed of cells with large distinct nuclei and by their lack of secretory activity. The cells of the mesonephric tubules do not take a mucicarmine stain, while those of the cervical glands stain vividly with mucicarmine.

The cells which line the tubules lying within the cervical musculature are similar to the cells of the fetal structures described above: there is a single layer of low cuboidal epithelium (Fig. 9) which has a clear translucent cytoplasm with a spherical to egg-shaped dark-staining large nucleus. When stained with iron hemotoxylin the nuclei stand out from the clear cytoplasmic background in a characteristic fashion. Mucicarmine staining shows little or no secretory activity, although occasionally a pinkish mass will be found within a tubular lumen. This is in sharp distinction to the epithelium of cervical glands of comparable size where the tall columnar epithelium contains long rod-shaped nuclei occupying but a small portion of the cell. The richness of secretory activity in the epithelium of the cervical glands is well presented by the vividness with which the cells take a mucicarmine stain.

Elongated narrow clefts with surrounding small tubules (Figs. 10 and 11) lying in the middle muscle layers of the cervix are most characteristic of all of the fetal remnants of the mesonephric ampulla in the adult cervix. These are counterparts of the spurs which the ampulla sent downward into the cervix in

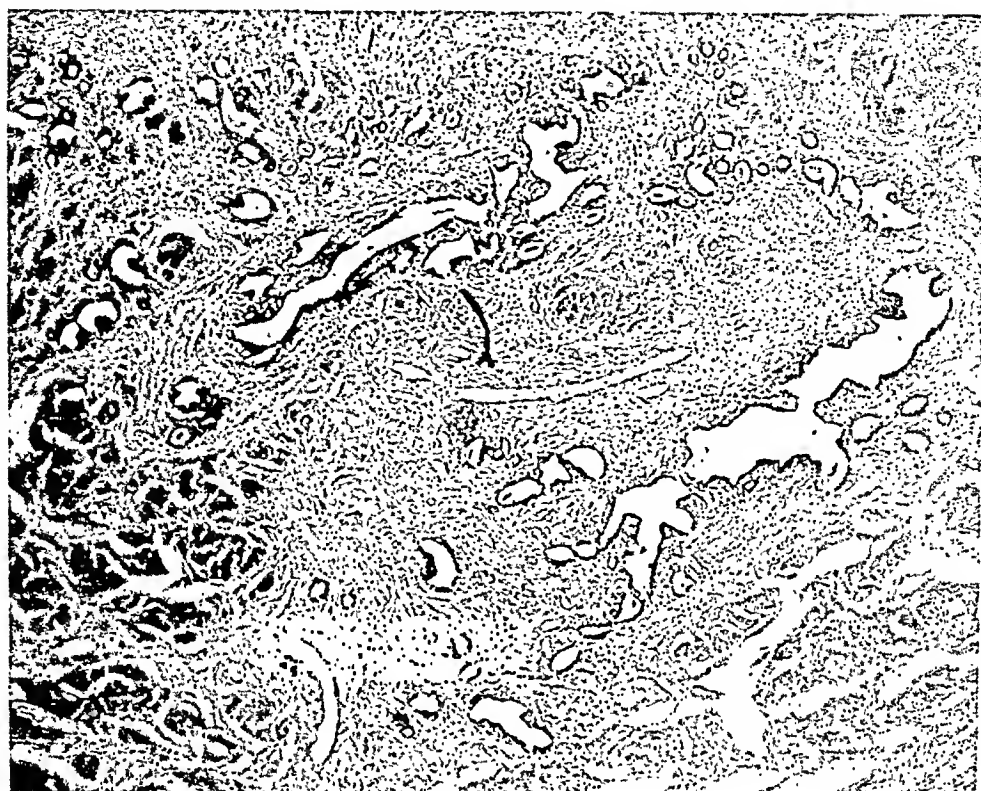


Fig. 8.—Remnants of the mesonephric duct in the adult cervix often occur as cystic dilations of the ampullar tubules with smaller tubules about them. This photomicrograph is from one side of a serially sectioned cervix which contained bilateral mesonephric remnants. (See Fig. 12.)

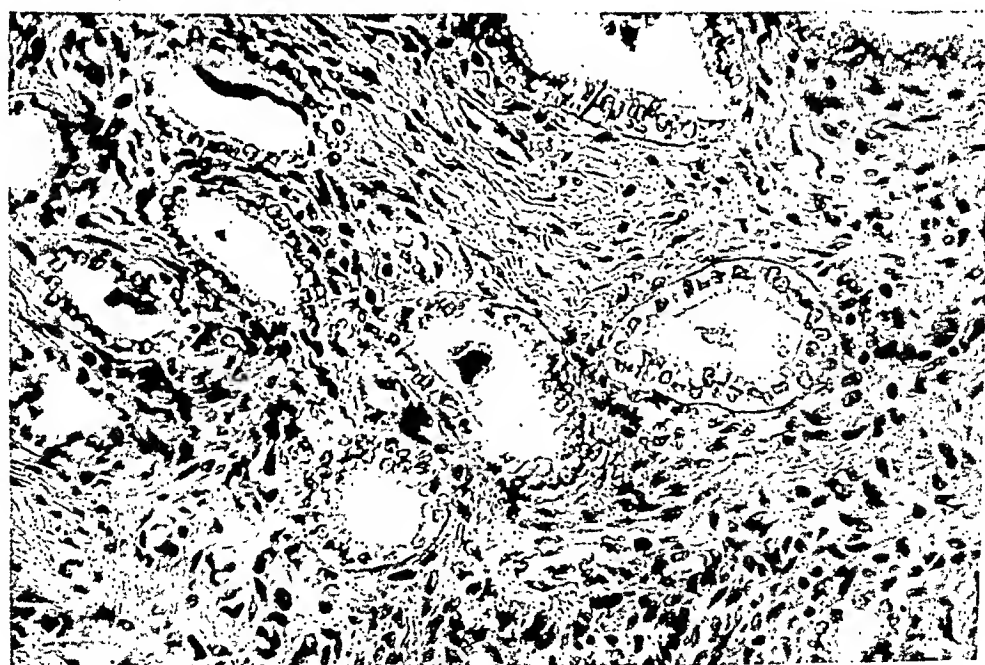


Fig. 9.—The mesonephric ampullar tubules in the cervix are lined by a single layer of low cuboidal epithelium whose cells have clear translucent cytoplasm and spherical or ovoid-shaped large dark-staining nuclei.



Fig. 10.—A longitudinal section through a cervix to show a mesonephric remnant in the mid-cervical wall. In this instance there is a persistence of a narrow cleftlike large tubule which is surrounded by numerous small canaliculi. (See Fig. 11.)



Fig. 11.—The cleftlike mesonephric passages in the adult cervix are remnants of the spurs which the ampulla sent downward into the fetal cervix. They have small canaliculi surrounding them. (See Fig. 10.)

late fetal life. The lining epithelium of these cleftlike structures resembles that of the tubules except that the columnar epithelium is often higher and the nuclei of the cells making up the epithelium tend to be more rod shaped.

Usually the persistent mesonephric remnants are found in only one wall of the cervix. However, in one serially sectioned cervix included in this report, bilateral cervical remnants were discovered (Fig. 12). In this specimen it was possible to follow the mesonephric duct structures from the vicinity of the internal os to the lower portion of the portio vaginalis. The tubules lay in the musculature of the middle portion of each lateral cervical wall. They corresponded in position and in structure to the fetal mesonephric ducts observed in serially sectioned embryonic uteri.

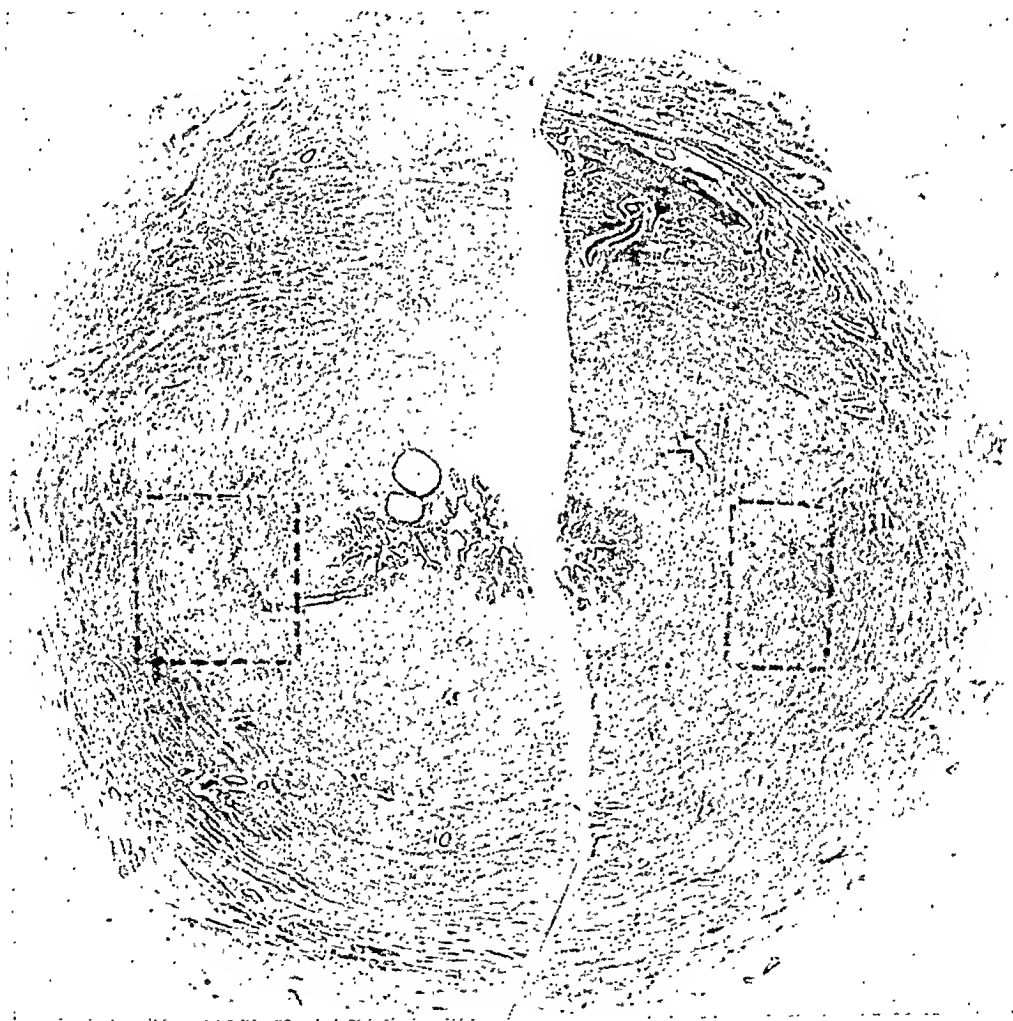


Fig. 12.—Cross section through the two halves of a serially sectioned adult cervix. The boxed areas contain bilateral persistent mesonephric duct tissue which has the same histologic structure as found in the fetus. (See Fig. 8.)

There is considerable variation in the reported incidence of persistent mesonephric ducts in the cervix. In a series of fifty-four adult uteri examined specifically for mesonephric remnants, Meyer found portions of the duct in twelve specimens. Rieder⁷ noted similar rests in 20 per cent of the specimens he studied. Maudach⁸ reported mesonephric rests in 40 per cent of the uteri from all newborn and older children he examined. Fischer,⁹ on the other hand, found a mesonephric duct in but one adult uterus of fifty which he inspected.

There were five nonneoplastic mesonephric duct remnants in the 1,192 specimens examined in this laboratory. In a series of 1,413 cervixes examined by Wolfe, "only one contained normal remnants of Gartner's duct." It would appear that the earlier workers held a unanimity of opinion as to the presence of mesonephric residues in the adult cervix but that they disagreed notably as to the frequency of such remains. They were in agreement in stating that these residues were for the most part comparable in structure with the mesonephric tissues found in the fetus near term. That neither Wolfe nor I found mesonephric tissues in the cervix with a frequency comparable with that of Meyer and others may be due to the fact that our specimens were from surgical pathologic material and that we had access to but one or two blocks cut from each cervix. It is quite probable that our incidence would more closely approximate Meyer's if we had serial sections from each of the cervixes in our series. In addition in the series reported here, all specimens difficult to differentiate (particularly where there were questionable tubules near the isthmic glands) were discarded.

It is necessary to differentiate between a simple remnant of a fetal structure in the adult and a neoplasm arising from such a tissue. Meyer¹⁰ makes this distinction particularly evident in discussing the persistence of mesonephric cervical remnants when he points out the difference between the factors leading to the prevention of the normal disappearance of fetal tissue (phylogenetic autonomy) and those factors leading to tumor formation (pathologic cellular autonomy).

Three types of neoplasms of mesonephric duct origin may be expected to develop in the uterus—cysts, adenomatous proliferations of varying degree, and adenocarcinomas.

A cystadenoma developing from rests of wolffian duct origin in the cervix is reported by Dworzak.¹¹ Henkel¹² described a "hypertrophica portiois cystica" which he stated was a cystic transformation of cervical rests arising from the wolffian duct. Stubler,¹³ Kuster,¹⁴ Arx,¹⁵ Combet,¹⁶ Knauer,¹⁷ Gudim-Lewkowitsch,¹⁸ Klein,¹⁹ von Recklinghausen,²⁰ and others have also reported cysts of the uterus which presumably were of mesonephric duct origin. Critical review of most of these case reports, however, makes it difficult to determine whether or not the neoplasms actually originated in the cervix or whether they developed in the lateral uterine wall.

Criteria have been established for the diagnosis of uterine cysts of mesonephric origin by Meyer, Dworzak, and Klein. They state that for such cysts to be topographically correct they should lie in the longitudinal axis of the uterus, they should have a serpentine or corkscrew course, and they should be lined by columnar epithelium characteristic of the lining of mesonephric structures; there may, in addition, be a scattering of surrounding muscle and stroma which resembles that surrounding the fetal mesonephric duct above the ampulla. One specimen in the 1,192 examined in this laboratory showed cystic cavitations in the lateral uterine wall beginning below the level of the internal os and extending upward in the myometrium to a point approximately midway between the internal os and the fundus (Fig. 13). The serpentine course of the cystic cavitations in the uterine wall and the low cuboidal epithelium lining the cystic cavities suggested that this was a cystic mesonephric duct remnant.

Meyer mentions that occasional isolated mesonephric ampullar tubules tend to be cystic. He states that while these cystic changes are occasionally found in the fetus, they are much more common in the adult. Rarely are the cysts larger than 2.5 mm. in diameter. Differentiation between these cysts and deeply placed isolated cysts of the cervical glands is not always easy. Mixed cysts may occur in which there is a fusion of mesonephric duct cysts with glands of the cervix.

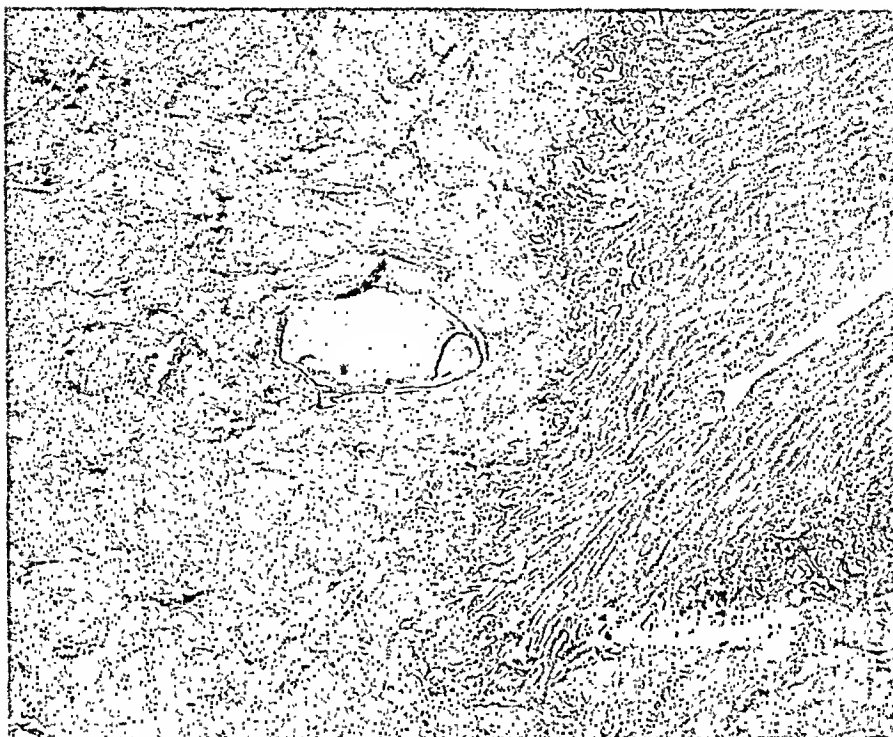


Fig. 13.—Photomicrograph through the uterine wall showing a cystic cavitation which, beginning below the level of the internal os, extended for a distance of 2 cm. cephalad. The irregular course of the cavitation and the low euboidal epithelium which lined it suggested that this was a cystic mesonephric duct remnant.

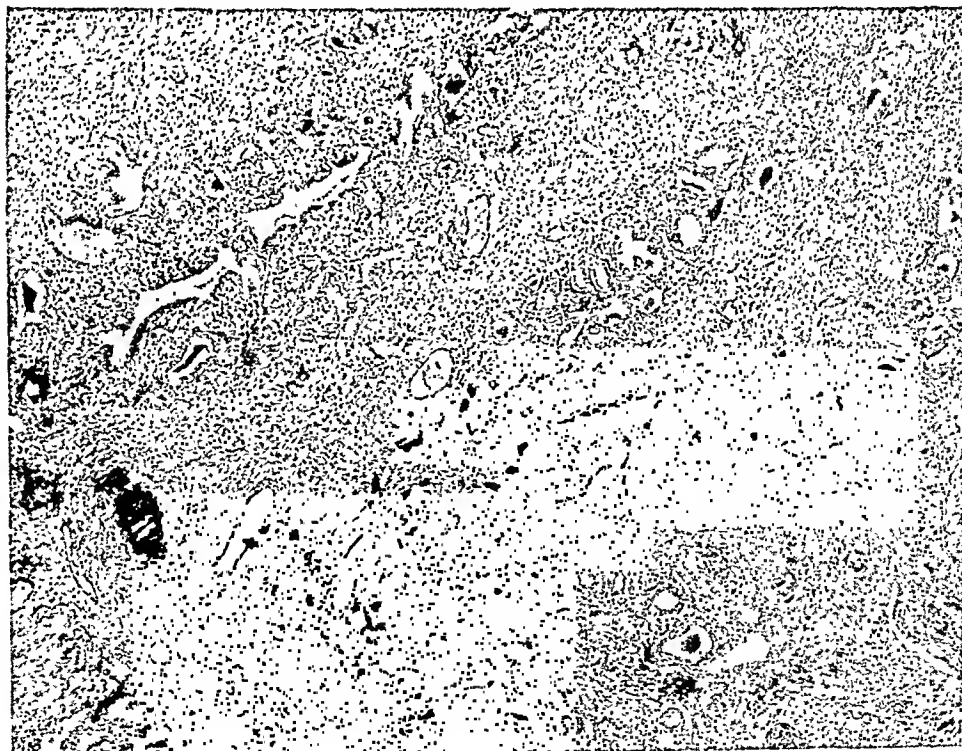


Fig. 14.—Adenomatous hyperplasia of mesonephric duct remnants in the cervix develops as masses of small tubules infiltrating the cervical wall. In this section through the mid-portion of the postero-lateral cervical wall minute tubules lie in groups throughout the musculature. (See Fig. 15).

Adenomatous hyperplasia of mesonephric duct remnants in the cervix occurs as a conglomerate mass of closely packed small tubules or canaliculi which may be found either near the cervical mucosa or, more often, in the middle layers of the cervical musculature (Fig. 14). These adenomatous proliferations rarely become tumors of appreciable size and are most often discovered in the course of histologic examination of cervical tissues removed either for biopsy or at the time of amputation of an unhealthy cervix. The tubules or canaliculi usually lie in groups in the interstices of the cervical musculature. There may be, however, occasional isolated masses of closely packed tubules near the endocervical mucosa. Microscopically the tubules are small and are round or ovoid in shape. While they may vary in diameter from capillary size to macroscopic cysts, a distinguishing characteristic which I have seen has been the tendency for most of the tubules to be approximately the same diameter. When larger tubules are present they may show outpouchings and diverticula. There is little or no musculature about the tubules and scanty or no stroma. When stroma is present, as described by Rust,²⁷ it is of a spindle or round cell character similar to that seen about the duct above the ampulla. Rarely a long narrow ductlike cleft will be discovered in the midst of an adenomatous proliferation; such a ductlike remnant may be the remains of the ampullar cleft seen in the fetus.

The tubules (Fig. 15) which comprise these adenomatous hyperplastic formations are lined by a single layer of cylindrical epithelium. The cells are low cuboidal in type and the individual cells contain a translucent pale cytoplasm with a large round or coffee bean-shaped nucleus which fills much of the cell body.

The nuclei are rich in chromatin and stain intensively. An occasional tubule will show some secretory activity as evidenced by a mucicarmine staining of its contained secretion; for the most part, however, the tubular lumina are empty and the cells do not take a mucicarmine stain.

Meyer, Klein, and Thumlin described cervical adenomas of mesonephric origin many years ago. More recently, Rust, Rockstroh, Reeb, and Wolfe have reported similar ones. In each of these reports the findings are essentially as described here both as to origin and structure of the neoplasm. In none was the diagnosis made prior to histopathologic examination of the excised tissues.

There were four cervixes which contained adenomatous hyperplasias of mesonephric duct origin among the 1,192 specimens examined in this laboratory. In one of these the major portion of the posterolateral cervical wall was infiltrated by innumerable minute twisted tubules having the typical histologic picture just described; the other three contained areas in which there were compact masses of canaliculi having a topographic location and microscopic appearance compatible with a diagnosis of adenomatous hyperplasia of mesonephric ampullar tubules.

Adenocarcinomas may develop from mesonephric duct remnants in the cervix. Grossly the tumor has usually been found (in those cases reported where the neoplasm had not as yet involved the entire cervix) in the anterolateral or posterolateral midcervical walls. The growth is a gray-white or brownish friable area which can be differentiated from the remainder of the cervix. Microscopically the tumor consists almost entirely of masses of glandlike tubules which are packed closely together. These tubules show an unorganized arrangement and are of varying sizes, many having distended lumina while the lumina of others are narrowed or obliterated by the many layers of cells forming the tubular wall. In some areas epithelial proliferations or papillary extrusions project into the tubular lumina. The cells and tubules lie in the fibromuscular connective tissues of the cervix and tend to invade between the muscle bundles.

The epithelium lining the tubules is bi- and multi-striated throughout and is marked by unusual irregularity in the height of the cells and the position of the nuclei. The cell nuclei are for the most part large lightly staining and contain an increased number of mitoses. Mucicarmine staining shows no evidence of any appreciable amount of mucus in the cells, but in many places the lumina have a thin mucuslike layer on the epithelial surface; this layer takes a light pinkish stain with mucicarmine.

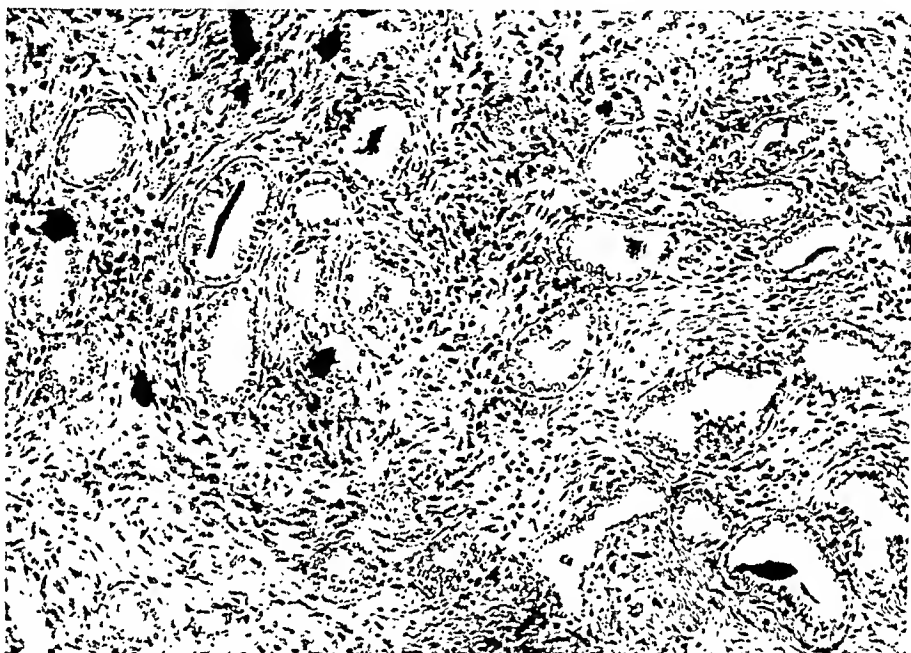


Fig. 15.—The tubules making up an adenomatous hyperplasia of mesonephric duct remnants in the cervix are often found in closely packed masses. They are lined by a single layer of low cylindrical or cuboidal nonsecretory epithelium, the cells of which have a pale cytoplasm and large round or ovoid well-staining nuclei. (See Fig. 14).

The first report of a carcinoma of the ampulla of the mesonephric duct was made by Meyer in 1903.²¹ The same author reported a second case in 1907.²² In the first instance the nature of the tumor was recognized by the fact that the upper part of the mesonephric canal was still intact and that the adenomatous glandular proliferation arising from it gradually merged into a destructive neoplasm of the cervix and portio which had the characteristics of the tumors described. The second case was histologically similar to the first. Danneel²³ also describes an adenocarcinoma of the cervix which was assumed to have developed from mesonephric duct remnants because of its position and structure. This opinion was concurred in by Meyer who saw sections of the neoplasm. Wagner, in 1929²⁴ and Rockstroh, in 1935²⁵ reported similar tumors.

One adenocarcinoma of the cervix having an architectural pattern suggesting origin from a mesonephric remnant was among the 1,192 specimens examined for this presentation. The tumor, discovered in routine sections, invaded but a small portion of the posterolateral wall of the cervix at the level of the internal os. It consisted of strands and masses of glandlike tubules (Fig. 16) extending into the substance of the cervix and invading the lower corpus. The lining of the tubules is composed of cuboidal and low columnar cells of irregular height having large pale-staining nuclei. There are numerous mitoses. In many places the configuration of the tubular structure is lost. The neoplasm invades between

the muscle fibers of the cervix. The assumption that this carcinoma developed from rests of mesonephric duct origin (insofar as such a diagnosis can be made in the absence of typical normal mesonephric tissue) is based on the position of the tumor and its architectural pattern. It shows no similarity to the usual malignancies arising from mucous glands. It has striking similarity in appearance to the case described by Meyer in which an adenocarcinoma could be identified as arising from a still intact mesonephric remnant.

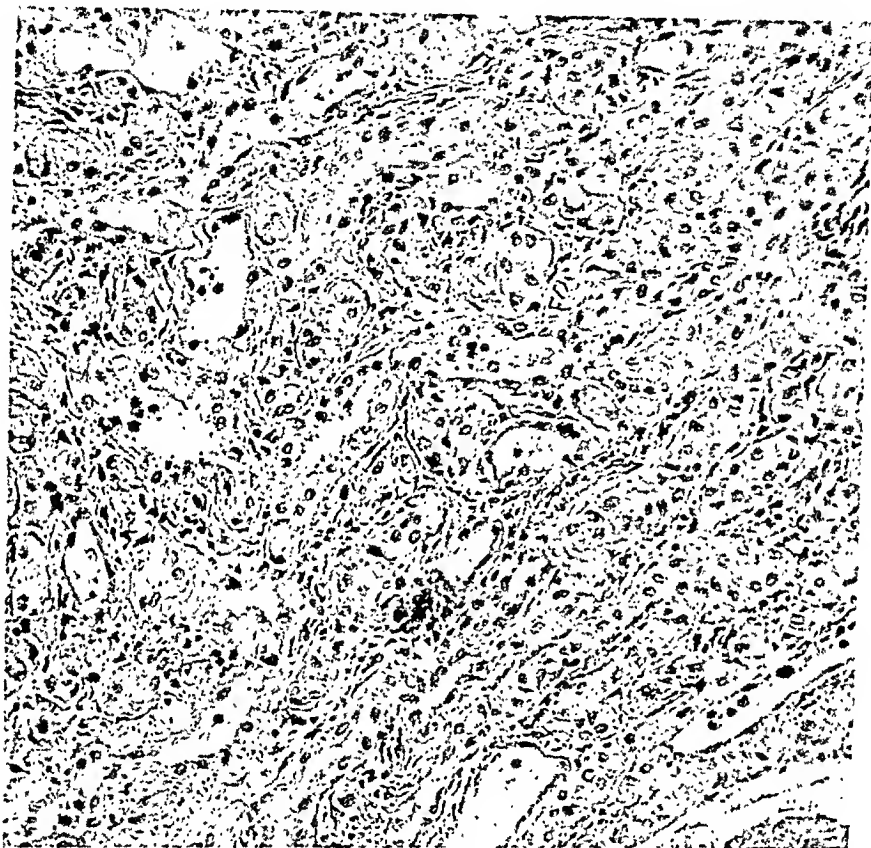


Fig. 16.—Adenocarcinoma of mesonephric duct origin in the cervix consists of masses of glandlike tubules which are closely packed. These tubules have a disorganized arrangement, are of varying sizes, and their lumina may be obliterated by many layers of cells.

Discussion

A fetal remnant which is homologous with a portion of the male genitals and which, instead of degenerating in a normal fashion, persists in the adult female should logically be diminutive in size and embryonic in character. The exact homology of the mesonephric ampulla in the female has not been demonstrated. The hypothesis has been advanced that it is homologous with either the ampulla of the vas deferens or the seminal vesicle. If this contention is accepted it would be assumed that tissues resembling the fetal mesonephric structures would be found. Furthermore it would not be anticipated that the development of the embryonic structures would progress beyond a late stage in female embryonic development. Rather, inasmuch as the remnants disappear

in most individuals, those which do occasionally remain, unless undergoing neoplastic changes, would tend to be small in size and poorly developed.

It is not within the scope of this presentation to attempt to explain why fetal remnants of the mesonephros persist in some women and not in others. Meyer has attempted an explanation of the phenomenon on the basis of the prevention of the normal disappearance of fetal parts by a particular stimulus located either in the vicinity of the fetal structure or else within the cells of the structure itself; this hypothesis is gone into in considerable length in his monograph entitled *Ueber epitheliale Gebilde im Myometrium einschliesslich des Gärtner-schen Ganges* published in 1899. That remnants of the mesonephric duct do persist in the fetal cervix has been well demonstrated by Meyer, Maudach, and Rieder. Study of serially sectioned fetal uteri reaffirm their observations. The definitive evidence in support of their efforts would be wax model reconstructions prepared from serial sections of the fetal and adult cervixes containing mesonephric remnants; such a project is at present under way in this laboratory.

A number of case reports have appeared during the past half century giving histologic descriptions of tumors similar to those first described by Meyer. There are now a sufficient number of these to warrant the acceptance of mesonephric duct remnants in the cervix as a histopathologic entity. In order to facilitate further investigation a table of published case reports is included herewith (Table I).

TABLE I. PUBLISHED CASE REPORTS OF MESONEPHRIC DUCT REMNANTS IN THE ADULT HUMAN CERVIX

| AUTHOR | REFERENCE |
|--|--|
| <i>Persistent Fetal Elements (Not Neoplastic)</i> | |
| Rieder, C. | Virchows Arch. 96: 100, 1884. |
| Maudach, F. V. | Virchows Arch. 156: 94, 1899. |
| Meyer, R. | Ztschr. f. Geburtsh. u. Gynäk. 42: 526, 1900. Ztschr. f. Geburtsh. u. Gynäk. 58: 527, 1906. |
| Wolfe, S. A. | Arch. f. mikr. Anat. u. Entwges. 73: 751, 1909. Am. J. Obst. & Gynec. 39: 312, 1940. |
| <i>Cysts of Mesonephric Duct Origin (Doubtful Omitted)</i> | |
| Dworzak, H. | Arch. f. Gynäk. 157: 162, 1934. |
| Henkel, M. | Arch. f. Gynäk. 113: 427, 1920. |
| <i>Adenomas</i> | |
| Meyer, R. | Ztschr. f. Geburtsh. u. Gynäk. 37: 332, 1897. Ztschr. f. Geburtsh. u. Gynäk. 42: 526, 1900. |
| Klein, G. | Virchows Arch. 154: 189, 1898. |
| Thumin, L. | Arch. f. Gynäk. 61: 15, 1900. |
| Rust, W. | Arch. f. Gynäk. 162: 350, 1936. |
| Rockstroh, H. | Ztschr. f. Geburtsh. u. Gynäk. 112: 95, 1935. |
| Reeb, M. | Gynéc. et obst. 36: 401, 1937. |
| Wolfe, S. A. | Am. J. Obst. & Gynec. 39: 312, 1940. |
| <i>Adenocarcinomas</i> | |
| Meyer, R. | Virchows Arch. 174: 270, 1903. Ztschr. f. Geburtsh. u. Gynäk. 59: 234, 1907. |
| Wagner, G. | Zentrallbl. f. Gynäk. 53: 1336, 1929. |
| Frohese, H. | Gesellseh. f. Gynäk., Berlin 12: 4, 1934. |
| Danneel, H. | Arch. f. Gynäk. 159: 395, 1935. |
| Rockstroh, H. | Ztschr. f. Geburtsh. u. Gynäk. 112: 95, 1935. |

In the classification of mesonephric remnants in the cervix differentiation should be made between nondegenerated fetal structures (occasional tubules, portions of persistent ducts, and scattered canaliculi) and new growths arising from such structures (cysts, adenomatous proliferations, and adenocarcinomas).

In 1,192 cervixes there were five specimens in which mesonephric remnants were found, one cyst of the cervicocorporeal uterine wall presumably of mesonephric origin, four adenomatous proliferations of mesonephric ampullar tubules, and one adenocarcinoma of the cervix which architecturally and topographically was of mesonephric origin. Detailed case reports have not been included because they are similar in all respects to the general description of each entity included in the text.

The diagnosis of a remnant of mesonephric tissue or a tumor arising from such a remnant will rarely be made grossly. The diagnosis is obviously a histopathologic one. It will be made for the most part during the course of histologic study of "routine" sections. If but one block of tissue is taken through the lower posterior lip of the cervix, as is customarily done in examining cervixes which are not suspected of harboring a malignancy, these interesting lesions will frequently be missed. It is quite probable that Meyer's statement that 20 per cent of all cervixes have mesonephric remnants in them is more nearly correct than the incidence of approximately 1 per cent that I am reporting.

The identification of typical mesonephric duct remnants in the cervix is not difficult. The location of the tubules in the midportion of the lateral cervical wall is characteristic. Characteristic also are the small rounded canaliculi lined by nonsecretory occasionally ciliated low columnar or cuboidal cells with their translucent cytoplasm and large, round, clearly staining nuclei.

Summary and Conclusions

This presentation is an attempt to portray the embryology, the histology, and the microscopic pathology of mesonephric remnants in the uterine cervix. In order to accomplish this the literature has been reviewed, serially sectioned tissues have been studied, and sections from 1,192 surgically excised cervixes have been examined.

The presence of an ampulla of the mesonephric duct in the fetal cervix has been demonstrated by Meyer and others. Study of serially sectioned fetal uteri confirms their observations. Remnants of these fetal elements may persist in the adult cervix either as nondegenerated structures or as neoplasms arising from such residues. These remnants will ordinarily be discovered during study of routine sections of the cervix. The characteristic histologic appearance of mesonephric remnants in the cervix is that of small tubules or canaliculi lined by a typical low columnar nonsecretory epithelium consisting of cuboidal cells containing a translucent pale cytoplasm and large well-staining ovoid or round nuclei. These tubules can be differentiated from cervical glands. The histopathologic appearance of neoplasms arising from these remnants is given in detail.

Five cases of mesonephric remnants in the cervix and five neoplasms arising from mesonephric remnants in the cervix are added to the literature.

There is now sufficient evidence to warrant acceptance of mesonephric duct remnants in the cervix as a histopathologic entity.

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20. v. Recklinghausen (quoted by Dworzak): Die Adenomyome und Cystadenome der Uterus und Tubenwandung, ihre Abkunft von Resten des Wolffschen Körpers, Hirschwald, Berlin, 1896.
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23. Danneel, H.: Arch. f. Gynäk. 159: 395, 1935.
24. Wagner, G.: Zentralbl. f. Gynäk. 53: 1336, 1929.
25. Rockstroh, H.: Ztschr. f. Geburtsh. u. Gynäk. 112: 95, 1935.
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28. Thunin, L.: Arch. f. Gynäk. 61: 15, 1900.
29. Froboese, H.: Gesell. f. Gynäk., Berlin 12: 4, 1934.

Discussion

HAROLD L. GAINEY, M.D., Kansas City, Mo.—Mesonephric duct remnants in the adult female are a phylogenetic anomaly. The cranial end is normally encountered in the mesovarium and the lateral third of the mesosalpinx forming the epoöphoron. Caudad in the vagina, it again appears in the more familiar form of Gartner's duct cysts. That wolffian duct remnants persist in the cervix "is less commonly recognized" as stated by the author and readily accepted by our own experience and with Wolfe's report of one in 1,413 cases. Wolfe's explanation for his low incidence and my inability in several large pathology departments to find one case is that in routine sections of the cervix the area likely to be affected is not studied.

Dr. Huffman in this excellent presentation has made a definite contribution to American gynecologic literature. His review of the literature and presentation of the results of studies resulting from serially sectioning 1,192 surgically excised cervixes are given. Five cases of mesonephric remnants in the cervix and five neoplasms (one malignant) arising from mesonephric remnants in cervix are added to the literature.

This paper should arouse interest in more extensive studies of the uterine cervix, and with the increase in complete hysterectomy, opportunities for such studies will be more frequent.

The morphologic and the cytologic characteristics have been clearly demonstrated and described. Outlined are such details as the presence of a muscular tunic with a stroma of

spindlelike cells above the ampulla and their absence or presence in small amounts below the ampulla. The character of the epithelial elements varying from a single layer of cylindrical cells with oblong rod-shaped nuclei to low cuboidal with ovoid nuclei, with failure to take nuclearmarmine stain, while the glandular structures of the cervix do, aids in identification and differentiation of these structures.

The anatomic and pathologic significance of this presentation can be readily accepted. The clinical significance may be even greater than would be suggested by the low incidence of occurrence, 1 per cent. Further studies of malignant tumors of the cervix, particularly adenocarcinoma, might possibly reveal a higher percentage having origin from this source. A recently studied, yet to be reported, mesodermal mixed tumor of the uterus, when reviewed in the light of this paper, contained some highly suggestive tubular structures.

I would like to ask Dr. Huffman his reaction to this thought.

DR. HUFFMAN (Closing).—I wish to thank Dr. Gainey for his discussion and wish I might have summarized the material I presented as adequately as he has done. Dr. Gainey's description of a mixed tumor of the uterus containing tubular elements strongly suggests that it originated from a persistent mesonephric duct remnant. Undoubtedly mesonephric remnants in the uterus are frequently missed in the study of "routine" sections. The rarity with which multiple sections are taken from supposedly normal tissues surely must result in many similar omissions of other equally interesting pathologic entities.

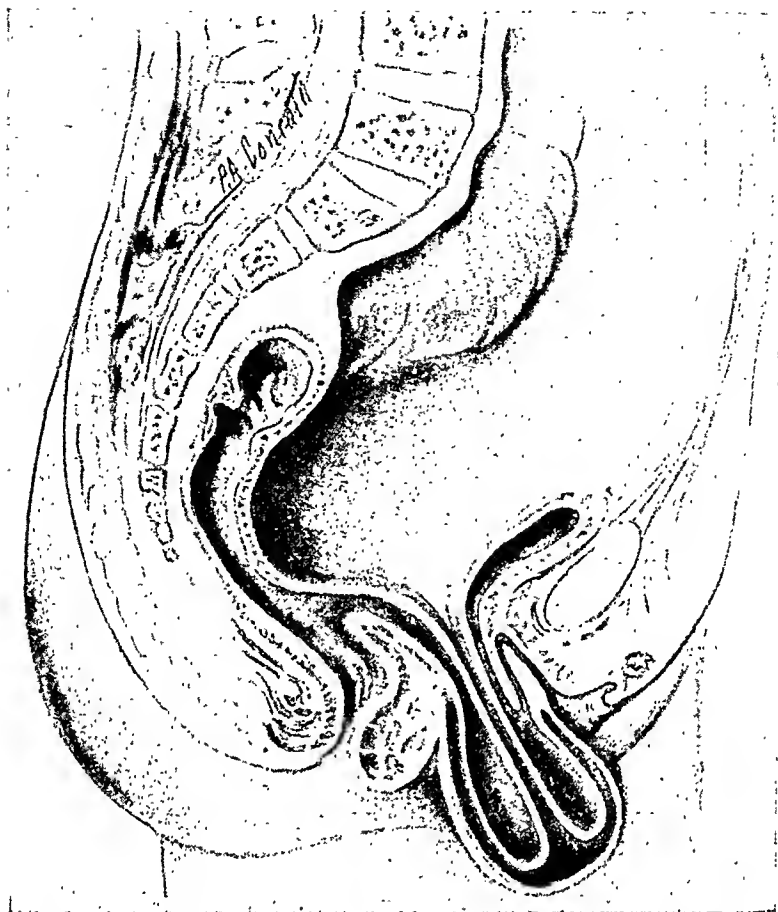


Fig. 3A.—Schematic illustration to show extent of potential visceral distortion when prolapse of vagina is complete. Kinking of urethra interferes with bladder function. Perineal body and rectovaginal septum are intact. Rectum is not involved in posterior vaginal wall hernia (enterocele).

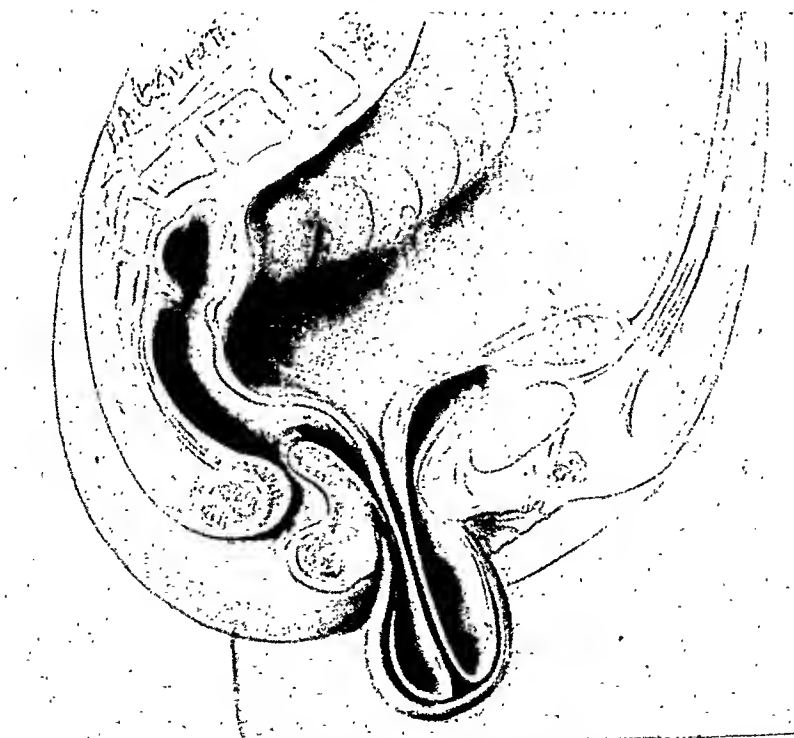


Fig. 3B.—Schematic illustration to show intimate connection between anterior vaginal wall and bladder as compared with that which exists between posterior vaginal wall and adjacent pelvic viscera.

enterocele (Figs. 3A and 4). It is important to differentiate between rectocele and enterocele because correction of these defects involves two entirely different operative procedures. High colpoperineorrhaphy is required for the former, while complete obliteration of the cul-de-sac, from above, may be necessary in the latter (Figs. 7 and 8). Both procedures may have to be employed if the two conditions coexist.

4. The rectum and vagina are less intimately connected than the bladder is to the anterior vaginal wall because the cellular tissue of the rectovaginal septum is flexible and lax, in order to adapt itself to the rectal movements involved in the act of defecation.

According to Demarest¹ the rectal supports are stronger than those of the bladder because the puborectal fibers of the levator ani are intimately connected with the rectum. Hence displacement of the posterior wall of the vagina and rectum has less significance, clinically, than the downward movement of the bladder with the anterior vaginal wall (Figs. 3A and 3B).

When looking at the condition from above after the abdomen is opened, the vagina is inverted and the walls descend toward the cervical stump or toward the vaginal cicatrix which is present if the patient has had a complete hysterectomy. A funnel-shaped arrangement is thus encountered with the cervical stump or vaginal cicatrix being in the most dependent position, comparable to the small end of a funnel (Fig. 1). The peritoneum descends into the vaginal funnel covering the bladder; then, after leaving the bladder, it extends on to the posterior wall of the vagina and is reflected upward on to the anterior wall of the rectum and sigmoid. Because the uterus has been removed, the cul-de-sac of Douglas may be elongated. This predisposes to the development of an enterocele. It may or may not be associated with rectocele, since the latter is dependent to a very great extent upon the functional efficiency and anatomical integrity of the perineal body and rectovaginal septum (Fig. 4).

Complete obliteration of the cul-de-sac should be done in these patients if the best ultimate result is to be obtained (Figs. 7 and 8).

Commentary

Berkely and Bonney¹² said, "The possibility of curing a case of prolapse in which the entire uterus has been removed, without narrowing the vagina to a degree which prevents sex relations, is practically nonexistent."

Palsey² reported a successful cure of prolapse of the urethra and bladder in a 15-year-old girl by anchoring the anterior wall of the bladder to the periosteum of the pubic bone, as described by Hepburn.³ In this case the defect was primarily urethral.

Phaneuf⁴ stated, "Subtotal colpectomy (LeFort operation) is useful in older women with total prolapse or inversion of the vagina following hysterectomy. The one disadvantage, namely, closure of the vagina, makes it applicable only to those women whose age make sexual relations unimportant." He reported a series of twenty-six cases of subtotal colpectomy and six cases of total colpectomy but he did not say at what age sexual relations become unimportant to women. We believe that colpectomy is unnecessary at any age if the condition of the patient will permit her to be subjected to an abdominal operation.

In the analysis of 730 operations for uterovaginal prolapse which he has performed over a period of twenty-seven years, Phaneuf says, "The rate or recurrence in all operations for prolapse will no doubt increase with the length of time that the patients are observed." He reports two cases of slight recurrence after using Moscheowitz' technique for the correction of a large posterior

vaginal wall hernia. "In neither case was further correction necessary." He goes on to say that "adequate repair of the pelvic floor is essential in all cases unless the perineum is intact and gives good support," and, "Subtotal or total colpocectomy are the only operations from which satisfactory results may be expected."

We would like to submit the "rectus suspension principle of crossed-suspender support" as a dependable surgical procedure in the treatment of complete prolapse of the vagina and bladder following hysterectomy for patients in whom an abdominal operation is not contraindicated.



Fig. 4.—First patient, fifteen months after operation. Shows relationship of enterocele to rectum, perineal body, and vaginal introitus. Ventral fixation of vagina has resulted in marked stretching of posterior vaginal wall, causing elongation of vulva and vaginal herniation. Normal relationship of bladder and urethra to symphysis is maintained. Perineal body and rectovaginal septum are intact.

Rectus Suspension Principle of Crossed-Suspender Support

The ability of the vaginal walls to stretch when subjected to strain, tension, or pressure is well known. When ventral fixation of the vagina is employed as the *only* means of correcting bladder prolapse, the ability of this muscular tube to maintain permanently the bladder in normal position behind the symphysis is subject to question. If the vesicovaginal connective tissue septum is intact, in good condition, and can be included in the ventral fixation sutures, the prognosis is better than if the fascia is thin, atrophic, torn, and separated.

In our first patient, ventral fixation offered a poor prognosis. Therefore another kind of support was sought that would be readily available, strong, dependable, adequate, and permanent. At the same time it would have to be sufficiently flexible to permit normal bladder function and not interfere with the sex life of the individual. Moreover, it had to be applicable to the development of a technical sequence that would safeguard the patient, particularly from the standpoints of risk, trauma, and operating time.

The rectus suspension principle of crossed suspender support, for both the vagina and bladder (Figs. 9 and 12), has fulfilled all of these requirements in every patient on whom it has been used to date.

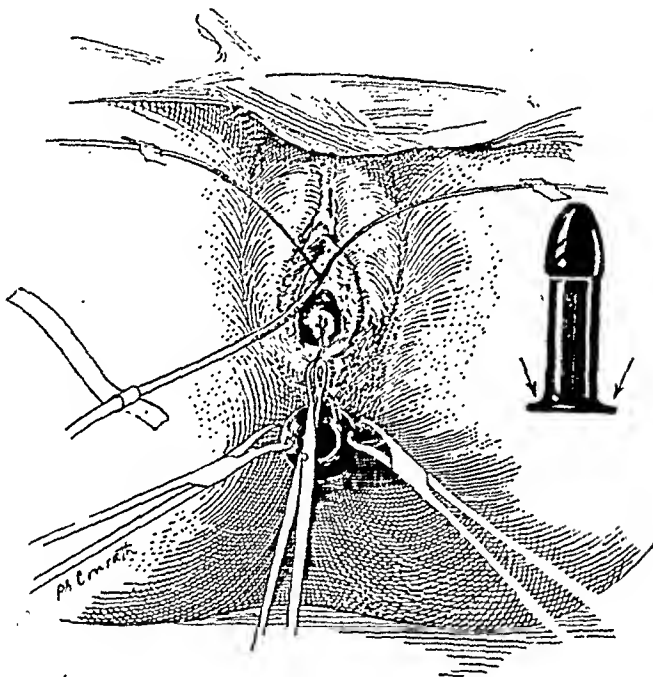


Fig. 5.—Preoperative preparation completed. Ureteral catheters in place. Bladder catheter connected with long tubing to permit distention during operation. Catgut suture in middle third of posterior vaginal wall is grasped with strong sponge forceps. Movement back and forth during closure of cul-de-sac facilitates accurate placement of purse-string sutures. Rectal dilator (inset) held in place with towel clips permits easy identification of relationships between rectum and surrounding structures. (Use of dilator suggested by Dr. A. P. Hudgins in a personal communication.)

Technique

Preoperative Preparation.—

Special features (Fig. 5):

1. Both ureters are catheterized to facilitate identification and thus prevent injury during closure of cul-de-sac.
2. A medium-sized hard rubber rectal dilator (Fig. 5) is inserted to facilitate identification of extent and relationship of rectum to vagina, levator ani, lateral walls of pelvis, coccyx, sacrum, and blood vessels. It is held in place by two towel clips inserted through holes bored at 9 and 3 o'clock and clipped to the perianal skin.

3. A loop of No. 2 chromic catgut is placed in the middle one-third of the posterior vaginal wall. It is firmly grasped by a strong sponge forceps which is left in place during the operation. By having this instrument moved back and forth when placing sutures for cul-de-sac closure, accurate identification of relationship to pelvic floor, blood vessels, ureters, and rectum is greatly facilitated (Fig. 5).

4. A retention catheter is placed in the bladder and connected to long tubing so that the bladder may be distended and emptied, by an attendant, during the operation (Figs. 1 and 5). This is particularly helpful when separating the vagina from the bladder because accurate identification of the bladder wall and ureterovesical junctions is greatly enhanced. Trauma to the bladder is minimized. Moreover, proper application of the strips can be assured if the bladder is distended during this phase of the operation.

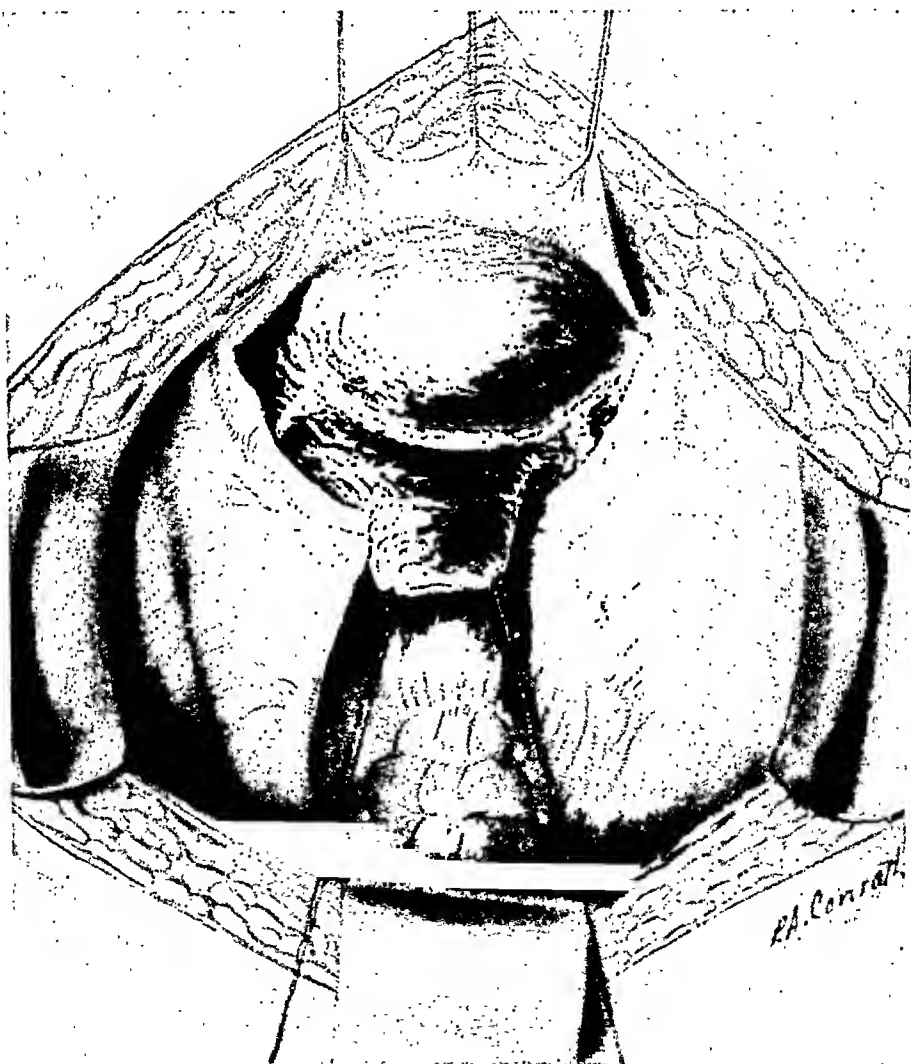


Fig. 6.—Traction sutures in peritoneal flap of bladder and cuff of vagina facilitate their separation down to level of ureterovesical junction on each side. Distention of bladder shows relationship to abdominal wall and vagina. Cul-de-sac is stretched and elongated.

Operative Procedure.—

The abdomen is opened through a midline subumbilical incision extending down to the symphysis. The intestines are packed off and the pelvis exposed.

Preparation of the vagina and bladder: The proximal end of the vagina is identified and pulled upward. The bladder peritoneum is reflected off the vaginal cuff or cervical stump, if present. Three traction sutures of heavy braided silk are placed in the peritoneal flap of the bladder. Two more are placed in the lateral limits of the vaginal cuff (Fig. 6). If the cervical stump is present it is circumcized and removed. The vaginal cuff is closed tight with chromic catgut before placing traction sutures. If ventral fixation is to be done, the cervical stump is not removed unless it is pathologic.

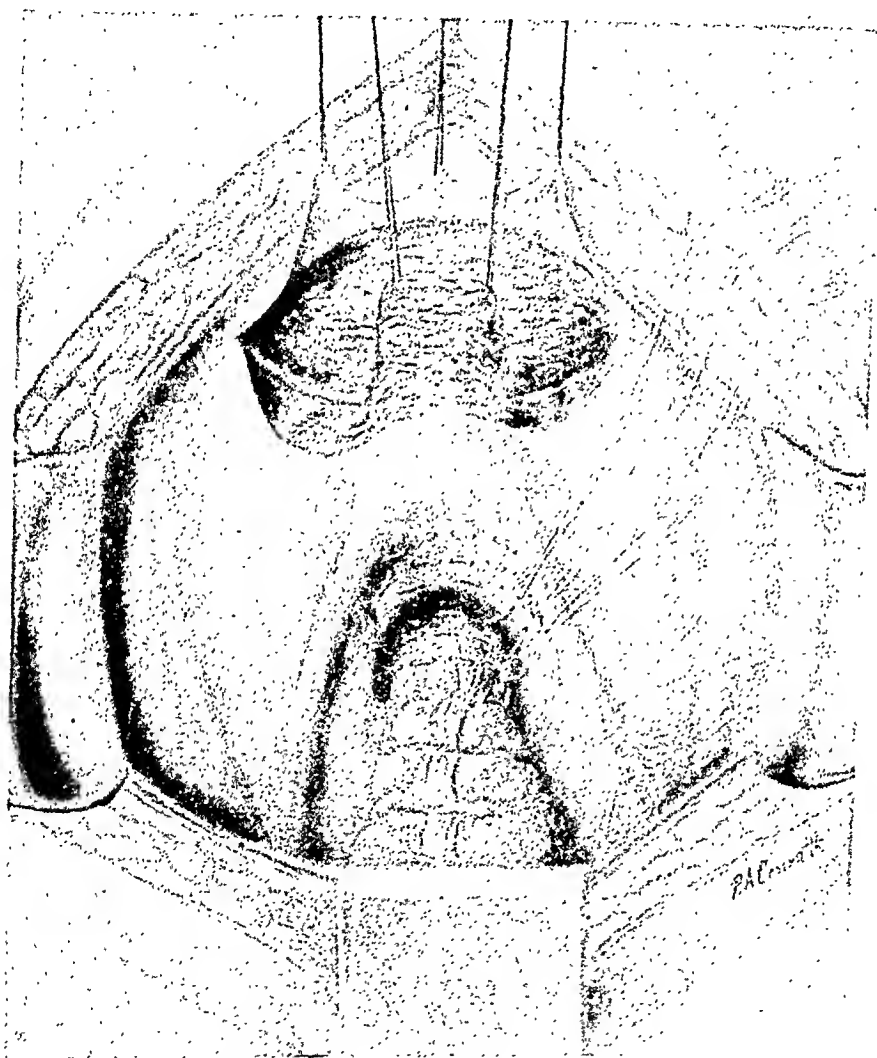


Fig. 7.—Closure of cul-de-sac below level of sacrouterine ligaments. Moschcowitz method of superimposed purse-string sutures which include posterior wall of vagina, rectum, and lateral pelvic walls. Each suture should be tied before the next one is placed.

Mobilization of the vagina and bladder: Traction on the bladder and vagina is applied in opposite directions and dissection is started. The anterior vaginal wall is separated from the bladder by blunt and sharp dissection down to the ureterovesical junction on each side. Trauma to the bladder wall is minimized as much as possible at the expense of increasing trauma to the vagina, if necessary. Intermittent distention of the bladder with antiseptic solution (1:2,000 aqueous Merthiolate) makes it possible to perform this part of the procedure with efficiency and dispatch. If the vaginal wall is accidentally

perforated a small drain may be inserted later or it can be closed with a simple through-and-through catgut suture. When the ureterovesical junction on each side is exposed, the bladder and vagina have been completely mobilized above the level of these landmarks (Fig. 6).

In the presence of scar tissue, bleeding is usually slight. If necessary it can be readily controlled with hot packs or a hemoplastic preparation.

We agree with Polk,¹¹ that extensive separation of bladder and ureters from the vagina causes far less hemorrhage than might be anticipated. He encountered moderate bleeding in only one of seventeen patients reported on. Bleeding was slight in all of the seven patients in our series.

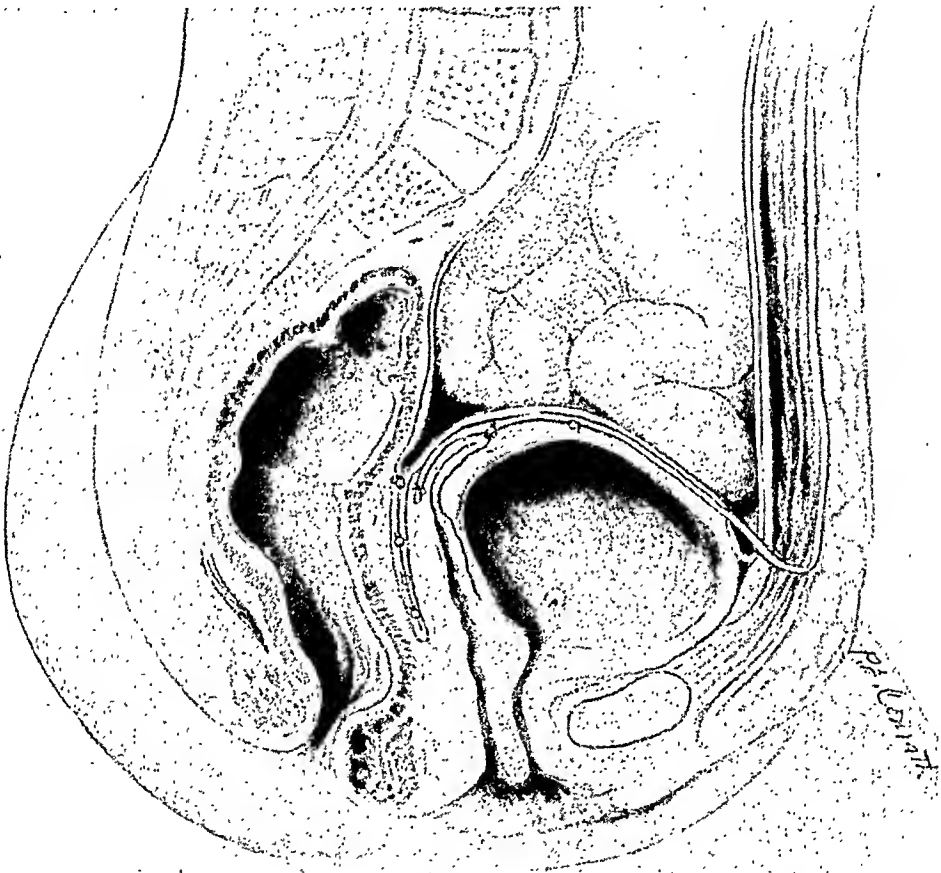


Fig. 8.—Vagina extends only short distance on to posterior bladder wall. Cul-de-sac closed below level of sacrouterine ligaments. "Crossed-suspender support" applied to bladder. Distal ends of strips sewed to posterior vaginal wall. Note separation of vagina from bladder down to level of ureterovesical junctions.

Closure of the cul-de-sac (Moschcowitz technique): After mobilization of the vagina and bladder, the cul-de-sac is closed. Moschcowitz,⁶ in 1912, introduced a method of superimposed purse-string sutures between the vagina, rectum, and lateral pelvic walls, placed in such a manner as to cause complete obliteration of the cul-de-sac (Fig. 7). He used it successfully in the treatment of prolapse of the rectum. It is equally applicable when utilized for the prevention or correction of a posterior vaginal wall hernia.

Nonabsorbable sutures are employed for closure of the pouch below the level of the sacrouterine ligaments (Figs. 7 and 8). The lowermost suture is placed about one inch above the inferior extremity of the cul-de-sac. Simi-

sutures, three to six in number, are passed through the peritoneum at intervals of 1 to 2 cm. until the level of the sacrouterine ligaments is reached. Each suture is tied before the next is placed. They pick up the peritoneum covering the posterior wall of the vagina, the lateral walls of the pelvis, and the anterior wall of the rectum. The folds of the sacrouterine ligaments are included in the uppermost suture (Fig. 7).

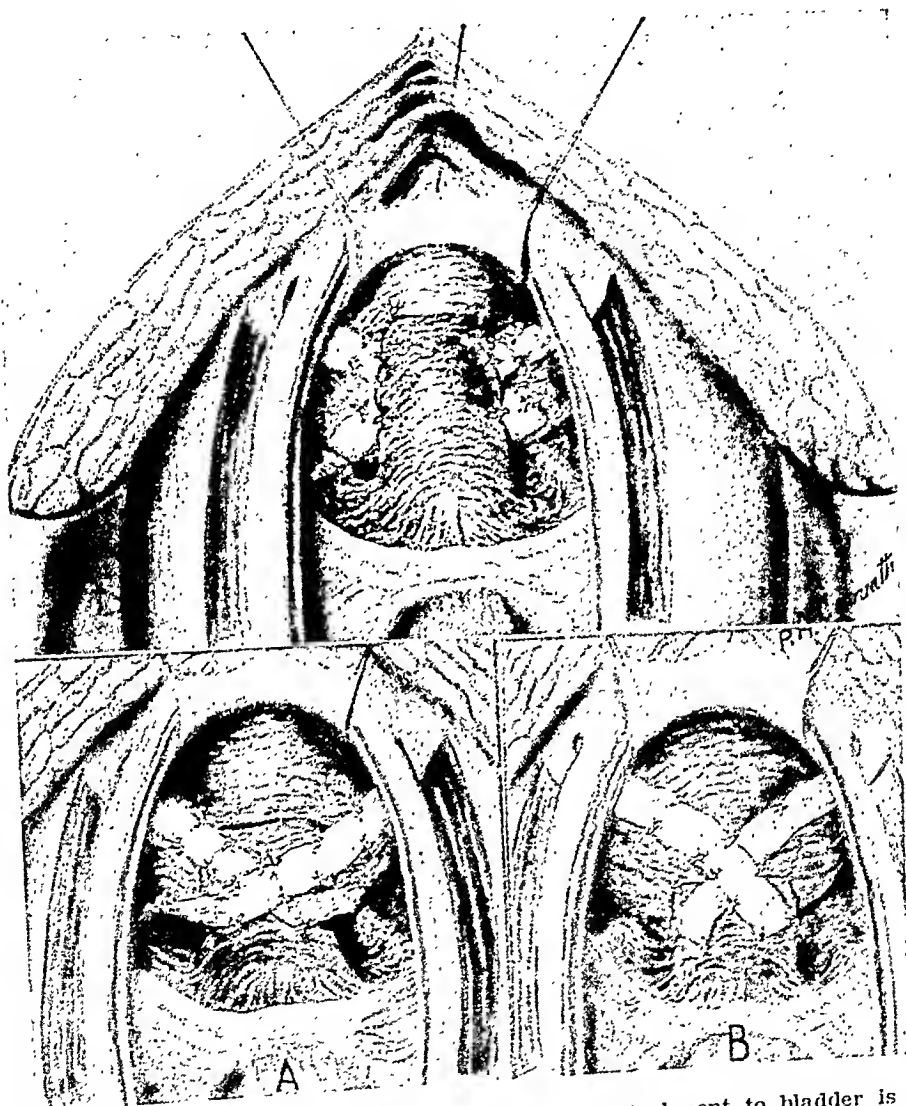


Fig. 9.—Vaginal vault sutured to strips after their attachment to bladder is completed. This method is applicable when vagina extends well up onto wall of distended bladder. It is to be preferred. When vagina extends only short distance onto posterior aspect of wall, it is included in distal ends of strips with "crossel-suspender support" applied to bladder (inset B). Strips may be crossed on posterior wall of vagina (inset A) when it extends between these two points; then ends are carried down to ureterovesical junctions and sewed to bladder.

When approaching the rectum, the sutures coming from the sides of the pelvis catch the serosal covering with firm, close stitches. This is done to prevent the possibility of subsequent intestinal herniation into the pouch through a defect between the walls of the rectum and pelvis. Two important structures must be avoided in placing these sutures: the ureters, which have been previously catheterized, and the internal iliac vessels, which can be readily identified by their pulsation.

This is a relatively simple procedure that requires about the same amount of time it would take to place an equal number of purse-string sutures elsewhere in the abdomen (Fig. 8).

Postoperative attention to bowels is the same as that employed in any other type of laparotomy.

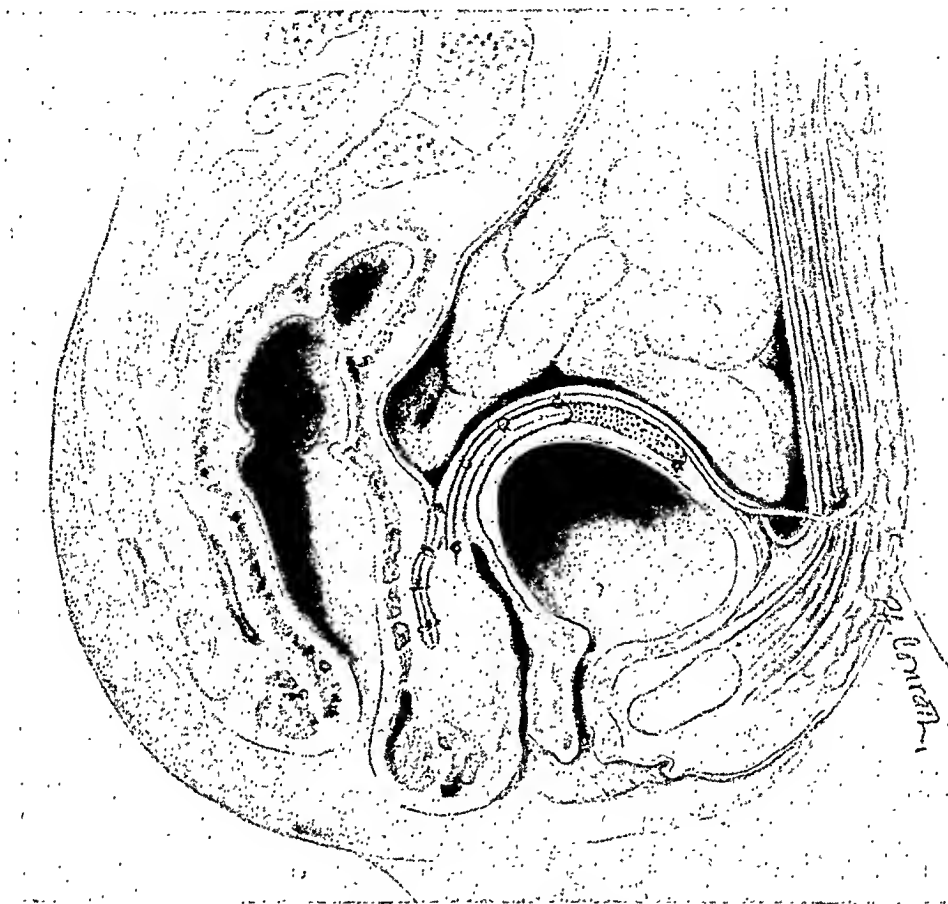


Fig. 10.—Vaginal vault is situated midway in relation to bladder; hence “support” is applied to posterior vaginal wall, and strip ends are sewed to bladder at level of ureterovesical junctions (not shown here).

Stippled area shows relationship of vagina when it extends well up onto bladder wall. Then it is sewed to strips after they have been applied to bladder (not shown here).

Criteria for determining the type of vaginal fixation to be used: After closure of the cul-de-sac, that part of the vagina situated above the level of the sacrouterine ligaments is still freely mobile. It may or may not be long enough to permit ventral fixation. This is determined before the next step in the operation is begun. If it extends only a short distance on to the posterior aspect of the distended bladder wall, it is included in the distal ends of the fascial strips, with the “crossed-suspender support” applied to the bladder (Figs. 8 and 9, inset B). If it extends well up onto the bladder wall, it is sutured to the strips after they have been attached to the bladder (Figs. 9, 10, stippled area, and 12). This seems to be the method of choice.

If the vaginal cuff is located between these two points, the “crossed-suspender support” may be applied to the posterior vaginal wall (Figs. 9, inset A, and 10), in which case the ends of the strips are sewed to the bladder if long enough (Fig. 9, inset A). Otherwise, they, too, remain in contact with the vagina. It is our impression that any one of these methods is preferable to

ventral fixation because the part of the vagina that is still unattached causes little or no additional strain to be placed upon the fascial supports. Moreover, if the vault is attached to the bladder musculature with one or two interrupted sutures of fine catgut, it does not interfere with normal function in any way (Fig. 9).

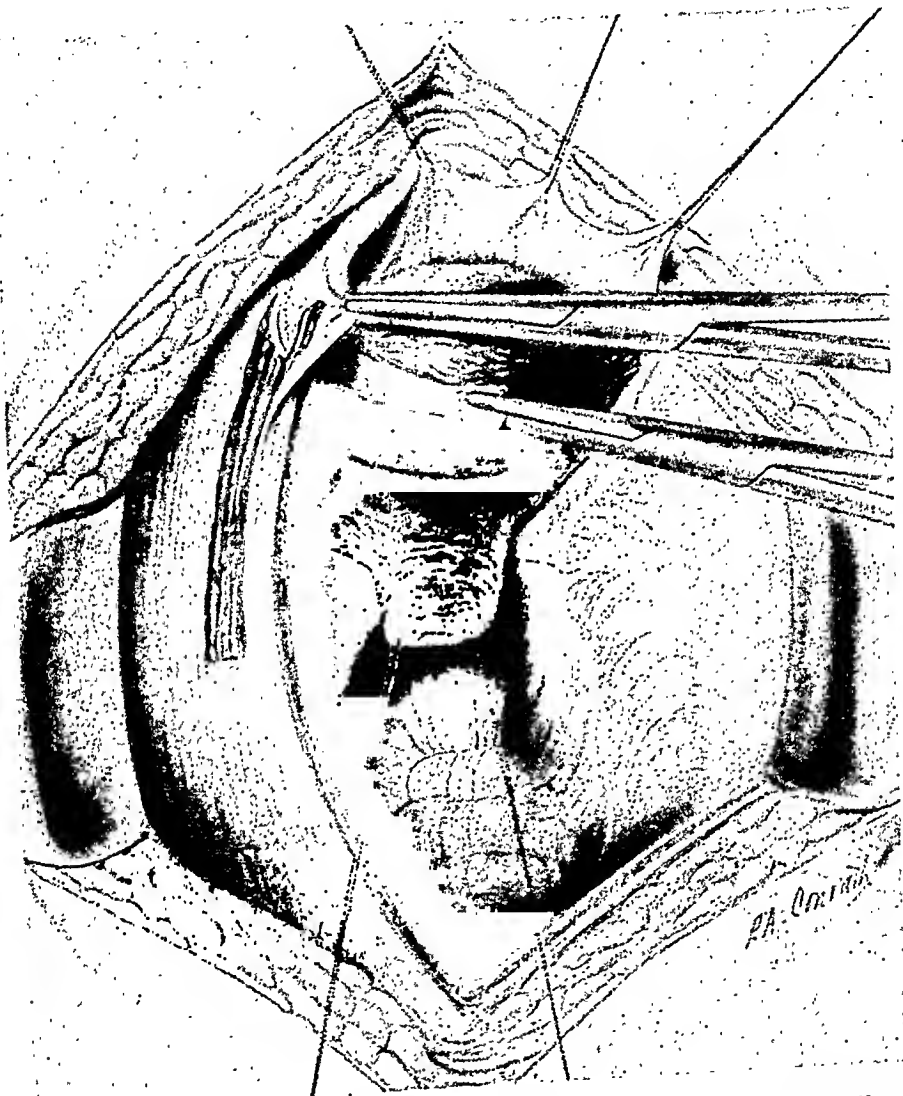


Fig. 11.—Fascial strip mobilized from anterior sheath of rectus is carried through muscle and parietal peritoneum down to ureterovesical junction on opposite side. Bladder is partially distended. Base of strip situated approximately 6 cm. above symphysis.

Mobilization and placement of the fascial strips: The anterior sheath of the rectus on one side is exposed. A fascial strip $1\frac{1}{2}$ cm. in width, approximately 8 cm. in length, and situated $1\frac{1}{2}$ cm. lateral to the cut edge of the fascia is mobilized in such a manner as to permit the base of the strip to be situated about 6 cm. above the symphysis pubis (Fig. 11). The strip must be long enough to reach the ureterovesical junction, on the opposite side, when the bladder is distended (Figs. 11 and 12). If the distal end is to be sutured to the vagina (Fig. 9, inset B) or the "crossed-suspender support" is to be applied to the posterior vaginal wall (Fig. 9, inset A), the strip should be long enough to

reach the level of the sacrouterine ligament *on the opposite side*. The strip may be lengthened or shortened by extending the base toward the symphysis with further incision or away from the symphysis by subsequent suture (Fig. 11). The base should be situated at or close to the point where the distending bladder first comes into contact with the anterior abdominal wall (Figs. 11 and 12).

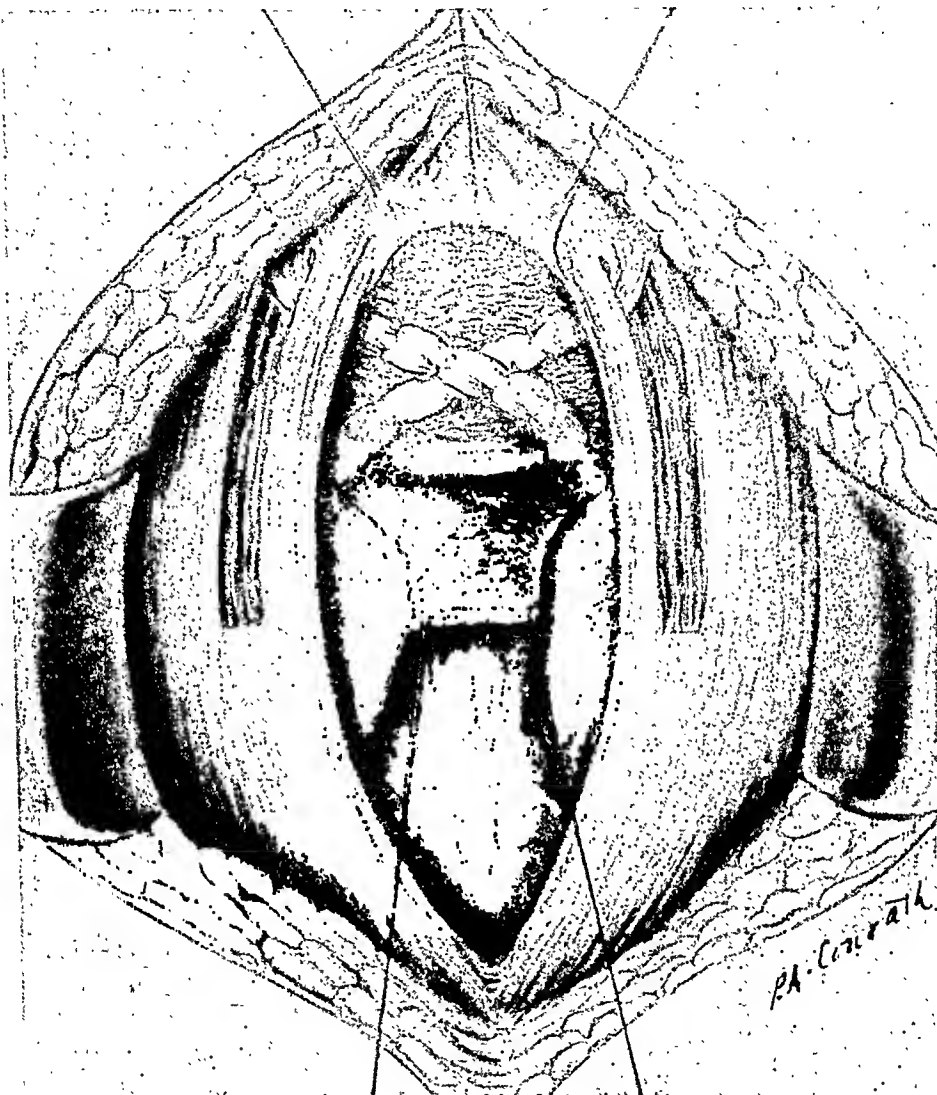


Fig. 12.—Shows "rectus suspension principle of crossed-suspender support." Strips are crossed as close to base of bladder as is conveniently possible. Relationship to bladder, as shown, is for purpose of demonstration. Ends of strips are in contact with, but not sutured to, ureters. Small rubber dam drain to vagina through accidental opening in wall.

The strip is carried directly through the muscle and parietal peritoneum and then down to the ureterovesical junction on the opposite side. When sutured in this position the distal end should be touching but not attached to the wall of the ureter. Interrupted sutures of fine nonabsorbable material, placed approximately 1 cm. apart, are used to attach the lateral borders of the strip to the muscular portion of the bladder wall (Fig. 12). Great care must be taken to be sure that the bladder mucosa is not included in any of these stitches. Partial distention of the bladder at this point is helpful. No. 34 alloy steel wire and fine linen have been used successfully. However, the choice of suture is a matter of individual preference so long as it is nonabsorbable.

After placement of the first strip is completed, the process is repeated on the opposite side in exactly the same manner. It is important to pay particular attention to two things:

First, the same degree on bladder distention must be maintained until both strips are in place, to be sure that subsequent bilateral support will be equalized (Fig. 12).

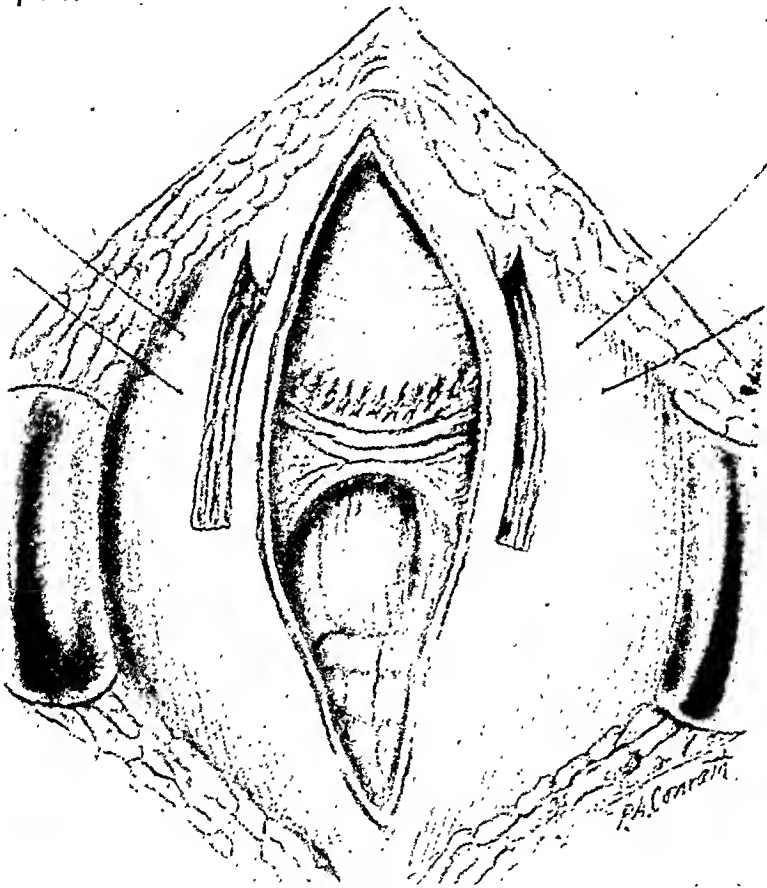


Fig. 13.—Peritonealization completed. Suture line shown here for purpose of illustration. Dome of bladder situated distal to bases of strips. Heavy silk sutures placed in anterior and posterior borders of cuff for ventral fixation of vagina.

Second, the location of the point at which the strips cross each other is decidedly important, because this is the point at which the greatest amount of support to the bladder is rendered. It should be situated on the inferior aspect of the bladder wall as close to the posterior border of the trigone as it is conveniently possible to get it. This is facilitated by taking the strips from the anterior sheaths of the fascia rather than from the medial borders. Although it causes the "crossed-suspender" effect to be rendered at a slightly wider angle, the point of greatest support to the bladder is more efficiently located. The possible theoretic increase in tension to which the bases of the strips may be subjected by their lateral relationship to the bladder is adequately compensated for by a more extensive distribution of support and by the fact that the degree of tension on the strips required to maintain normal visceral pelvic relationships is subject to wide variations, being directly influenced by changes in intra-abdominal pressure, differences in degrees of contraction and relaxation of both rectus muscles, and the amount of urine present in the bladder (Fig. 12).

Peritonealization: All raw surfaces are covered with bladder peritoneum. It is also sutured around the strips at the points where they penetrate the anterior parietal peritoneum (Fig. 12). The relationship of the bladder to the abdominal wall and adjacent strips is such as completely to obliterate any pockets into which loops of intestines might subsequently find their way (Fig. 13).

Technique of ventral fixation: If ventral fixation of the vagina is done, two heavy braided silk sutures are placed in the anterior and posterior borders of the vaginal vault or cervical stump and then brought out through the abdominal wall lateral to the defects in the rectus sheaths (Fig. 13). They are tied on each side and then crossed and tied in midline before closure of the skin and subcutaneous tissue (Fig. 14).

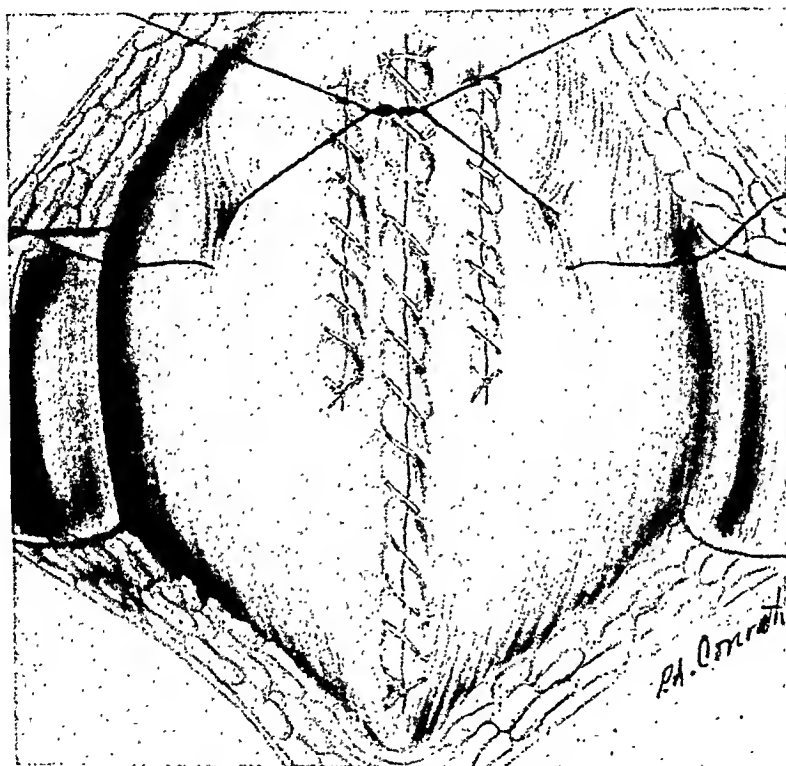


Fig. 14.—Strip defects closed with continuous catgut. Fascia closed with interrupted nonabsorbable sutures (not shown here), preferably cotton or wire, to safeguard against subsequent development of incisional hernia. Ventral fixation sutures are tied on each side (not shown here) and then crossed and tied in midline before closure of skin and subcutaneous tissue.

Closure of the abdomen and fascial defects: When the vagina is attached to the fascial strips, the peritoneum is closed in the usual manner without drainage. The defects in the rectus sheaths are closed with continuous chromic catgut. The fascia is closed with interrupted nonabsorbable sutures, preferably cotton or wire, as an additional safeguard against incisional hernia later on. Catgut may be used to approximate the sheath defects because they are protected by the underlying muscles (Fig. 14).

Postoperative Treatment.—Postoperative treatment is routine except that continuous bladder drainage is maintained for at least six days. When discontinued, careful precautions must be taken to be sure that subsequent overdistention does not occur. Most patients are able to void after the seventh day. Then a check is made for residual urine every twelve to twenty-four hours,

depending upon the fluid intake and output, until the amount obtained is less than 100 cubic centimeters. Routine catheterization technique is used. When it is no longer necessary, the patient is advised to empty the bladder every six hours or just as soon as she begins to notice a slight pressure or discomfort in this region.

Discussion

1. The first patient in this series had developed an enterocele fifteen months after operation. Two small incisional hernias were noted six and one-half years later, but the defects in the anterior rectus sheaths were intact. She was taken to the operating room again. At this time the enterocele, which had now been present for almost six years, was corrected by obliteration of the cul-de-sac. The bladder was still situated snugly behind the symphysis. The vagina had become intimately incorporated into the bladder wall by adhesions so dense that identification of the upper third was almost impossible. The fascial strips were intact and functioning. They were not stretched or elongated. On the contrary, they had been reinforced considerably by fibrous bands of postoperative adhesions between the anterior abdominal wall and that part of the superior wall of the bladder that was immediately adjacent. The strip on the left was difficult to identify because of the density of the adhesions. It would have been impossible to displace the bladder had we wanted to. The anterior wall and dome of the bladder were in normal position in relation to the pubovesical space and the lower abdominal wall.

2. We now prefer to suture the vagina to the fascial strips, whenever possible (Fig. 9). The "crossed-suspender support" can thus be applied more effectively to the base of the bladder and the ureteral junctions (Fig. 12) than when it or the ends of the strips are attached to the posterior wall of the vagina (Figs. 9, insets A and B). After suspension of the bladder is completed, the anterior wall and cuff of the vagina are sutured to the posterior aspects of each strip with interrupted catgut sutures (Fig. 9). If additional fastening seems advisable, the vault may be stitched to the bladder musculature, using one or two interrupted sutures of fine catgut (Fig. 9). This was done on one of our patients in whom bladder function was not affected.

3. Ventral fixation of the vagina was performed on the first patient because the tube was long, thin, and relaxed (Fig. 4). Moreover, it was decided to minimize the pull on the strips until a period of observation would permit consideration of the advisability of increasing their load with that part of the vagina situated above the level of the sacrouterine ligaments. Obliteration of the cul-de-sac was not done on this patient until six years later (Figs. 2 and 4).

After fifteen months of observation, during which time the fascial strips were apparently unaffected by prolonged periods of increased strain and pressure, it was decided to employ the same principle again with modifications (Fig. 9).

4. Obliteration of the cul-de-sac (Fig. 7) was considered essential in the second patient because the first patient had acquired a well-developed posterior vaginal wall hernia (enterocele) fifteen months after operation (Fig. 4). She

had no rectocele because a colpoperineal repair had been performed when the uterus was removed and she still had a good result (Figs. 2 and 4). The second patient had a small rectocele but no enterocele; therefore, a colpoperineorrhaphy was done first under local infiltration anesthesia. Then the abdomen was opened under general anesthesia and the operation herein described was performed (Figs. 12 and 9), including obliteration of the peritoneal pouch of Douglas (Figs. 7 and 8).

5. Approximately six years have elapsed since the second operation, during which time this principle has been used in five additional cases. In one patient the distal ends of the fascial strips were approximated to the vagina after the "crossed-suspender support" had been applied to the bladder (Fig. 9, inset *B*). In another the "support" was applied to the posterior vaginal wall while the ends of the strips were carried down to the ureterovesical junctions and sewed to the adjacent bladder musculature (Fig. 9, inset *A*). In the other three the vagina was sewed to the fascia and bladder musculature (Fig. 9) after vesical application of the "support" and strips (Fig. 12). We now have four cases in this latter category, one of each in the second (Fig. 10, insets *A* and *B*), and one, the first, in the ventral fixation group (Figs. 4, 13, and 14).

6. Because we appreciate the fallibility of any operation for vaginal prolapse that has not been subjected to long periods of follow-up observation, we have refrained from previous publication of this method. We do so now, only with the hope that it will be used by others who will help to discover its defects. We agree with Miller,¹³ that "in all new and untried procedures there are faults to overcome and minor difficulties to be ironed out."

7. The operation was performed for the first time over seven years ago. To date we have a series of seven patients in whom this principle has been used for the treatment of complete prolapse of the vagina and bladder following hysterectomy.

Summary

Seven Cases Are Available to Date.—

CASE 1.—Operation, 1940. Support to bladder. Ventral fixation of vagina (Figs. 12 and 13). Posterior vaginal wall hernia developed fifteen months later (Fig. 4). Two small incisional hernias discovered six years later. Otherwise result good (Fig. 2).

Second operation, 1947. Closure of cul-de-sac for treatment of enterocele. Repair of incisional hernias. Result good to date.

CASE 2.—Operation, 1941. Support to bladder. Vagina sewed to strips. Cul-de-sac closed (Fig. 9). Still being observed. Result good to date.

CASE 3.*—J. B. Operation, 1942. Support to bladder. Strip ends to posterior vaginal wall (Fig. 9, inset *B*). Cul-de-sac closed. Result good after nine months. No contact since.

CASE 4.*—R. G. H. Operation, 1943. Support to bladder. Vagina sewed to strips (Fig. 9). Cul-de-sac closed. Good result after three months.

Contact re-established three years later. Result still good to date.

CASE 5.*—R. G. H. Operation, 1943. Support to vagina. Strip ends to bladder. (Fig. 9, Inset *A*.) Result good after 3 months. No contact since.

CASE 6.*—M. F. Operation, 1944. Support to bladder. Vagina to strips (Fig. 9). Cul-de-sac closed. Good result after four months. No contact since.

CASE 7.—Operation, 1946. Support to bladder. Vagina to strips (Fig. 9). Cul-de-sac closed. Still being observed. Result good to date.

*Performed while in the A.A.F. Armed Services.

Conclusions

Additional cases and longer periods of observation will be necessary before conclusive evidence can be substantiated.

The author wishes to express his gratitude and appreciation to Mr. Philip A. Conrath, Art Department, St. Louis University School of Medicine, for his excellent work in preparing the illustrations contained herein.

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634 N. GRAND AVENUE.

Discussion

DR. NORMAN F. MILLER, Ann Arbor, Mich.—Dr. Fletcher has described and offered for our consideration a new operation for the correction of complete inversion of the vagina and its concomitant cystocele following hysterectomy. There are a number of operations for the correction of this condition such as ventrofixation, LeFort colpocleisis, correction of the cystocele enterocele, plus vaginopexy, none of which is entirely satisfactory. Although I have not used Dr. Fletcher's technique I am impressed by his reported results and the potentialities of his operation.

Since muscle is a basic element in support, it is odd that vaginal inversion should occur, even though rarely, if, during hysterectomy, the musculofascial paravaginal tissues, the cardinal, round, and sacrouterine ligaments, are called upon to give support to the remaining cervix or vaginal apex. Perhaps failure to use these structures accounts for the occasional vaginal inversion encountered. Whatever its etiology, however, the condition does occur and Dr. Fletcher has advocated the use of fascial strips taken from the rectus sheath as a means of providing support for the bladder and vagina.

In the past the use of fascia has not played a prominent part in the correction of gynecologic conditions. Perhaps we have overlooked a useful source of support with which we may achieve permanent relief for some of the gynecologic relaxations. The use of fascia in the management of urinary incontinence represents one application and now this operation gives us another field of fascial usefulness. Just how long transplanted fascia continues functional remains to be determined. Dr. Fletcher's observations in this connection have been favorable. Others have reported permanence of transplanted fascia. My own experience in this connection has not convinced me of its durability. In several patients treated for urinary incontinence by means of fascial transplant, I have failed to find the fascial strips some years later at the time of reoperation for the original symptom. Doubtless, time and further experience will answer this question.

Dr. Fletcher has emphasized the importance of differentiating between rectocele and enterocele in patients with inversion of the vagina. The desirability of eliminating the cul-de-sac of Douglas at the time of operation also seems entirely logical and sound.

It is interesting to note that in spite of the fact that this operation is primarily a bladder support, no disturbance of bladder function is reported.

In studying the diagrams of the operation I am not convinced that the excellent drawings correctly illustrate the final result. Thus, if Fig. 4 illustrating the result fifteen months after operation actually portrays the end result, then I fail to see how or why the vagina or bladder are supported. Collapse of the bladder in Fig. 4 would seem to permit descent of bladder, vagina, and cul-de-sac. Since Dr. Fletcher's results with this operation have been satisfying to him, I take it Fig. 4 does not correctly illustrate the postoperative relationships.

In his present technique Dr. Fletcher uses fascial strips from the rectus sheath approximately 3 cm. apart. Fascial strips taken much further apart, as from the external oblique, or, more easily, as a transplanted strip of fascia lata, would, it appears to me, make for vastly better support. Thus, a strip of fascia lata extending from one internal inguinal ring to the other paralleling the subperitoneal course of the round ligaments would provide good support and offer the added advantage of permitting an entirely normal direction to the supported vagina without the possibility of interfering with bladder function. I hope Dr. Fletcher will consider this variation in some of his future cases.

To me this has been an interesting report and the author deserves much credit for his originality in conceiving the technique and for his restraint in waiting seven years for reasonable proof of adequacy before recommending it for our consideration.

DR. FLETCHER (Closing).—Obviously, the drawings were made primarily to illustrate the principle involved. To do this it was not possible to include all technical details in some of the pictures. For instance, the "crossed-suspender support" is shown situated higher up on the bladder than it actually is when the bladder is not distended.

Four of the patients in this series are still being observed. One was followed for three months, another for six months. A third was seen three months after operation and then lost. Contact was re-established three years later. She still has a good result from the operation performed in 1942.

The extent to which the procedure can be accurately evaluated still has to be established. We are trying not to be too enthusiastic. We do not see this type of case very often, but eventually we hope to have the opportunity to accumulate a sufficient number of patients to warrant careful evaluation of the principle of "crossed-suspender support" for what it is actually worth or not worth.

✓**CESAREAN SECTION IN DETROIT DURING 1945—A COMPARISON WITH 1925 AND 1930***

HAROLD C. MACK, M.D., AND R. S. SIDDALL, M.D., DETROIT, MICH.

(From Wayne University College of Medicine)

PREVIOUS studies of the cesarean sections performed in Detroit which were made by Welz¹ and Seeley² for the years 1925 and 1930, respectively, showed a marked reduction in mortality during the intervening five years. In view of the steady decline in maternal mortality and the great improvement in the results of surgery in recent years, an analysis was made of cesarean sections performed during 1945, to determine the results of abdominal delivery in this city as compared to fifteen and twenty years ago. It was hoped that such a study would throw light on the means for further improvement.

In Detroit there were 36,100 live births for the year 1945, 32,634 during 1930, and 32,054 in 1925. As seen in Table I, there was a marked increase in the proportion of hospital deliveries during the twenty years. This change should be taken into account later when the comparative incidence of cesarean section for the individual hospitals in the different periods is considered. Table I also shows the deaths for the three periods, with noteworthy reduction in both maternal and infant mortality rates.

TABLE I

| | 1925 | 1930 | 1945 |
|-----------------------------|----------|------------|-----------|
| Live births | 32,054 | 32,364 | 36,100 |
| Total births | 33,416 | 34,007 | 37,028 |
| Birth rate | 25.7 | 20.6 | 21.4 |
| Births in hospitals | 32.2% | 44.5% | 94.3% |
| Maternal deaths | 219 | 215 | 58 |
| Maternal death rate | 6.8 | 6.6 | 1.6 |
| (per 1000 live births) | | | |
| Infant death rate | 80.1 | 64.7 | 33.6 |
| (per 1,000, under one year) | | | |
| Cesarean sections | 154 | 203 | 1,000 |
| Frequency | 1 in 217 | 1 in 167 | 1 in 37 |
| Maternal deaths | 20 (13%) | 9 (4.4%) | 8 (0.8%) |
| Infant deaths | 17 (11%) | 26 (12.8%) | 78 (7.8%) |

In the same Table I are given the actual numbers of cesarean sections for the years 1925, 1930, and 1945, as well as the frequency among the total number of births which these figures represent. It will be noted that this frequency had so increased that, by 1945, cesarean section was employed nearly six times as often as in 1925. It is equally remarkable, however, that the mortality rate of the operation in 1945 was only one-sixteenth that of 1925, and less than one-fifth of that in 1930. Actually, the 1945 death rate for abdominal delivery was

*Read before the Central Association of Obstetricians and Gynecologists on Oct. 25, 1947, in Louisville, Ky.

only slightly greater than the official maternal death rate fifteen and twenty years before. However, due to the great reduction in the general maternal risk, it is still five times the over-all maternal mortality for 1945. On the other hand, the infant death rate for cesarean section showed only moderate reduction. These differences will be subjected to further analysis later.

Table II shows the variations in the incidence of cesarean sections for the hospitals with 1,000 or more deliveries in 1945. There is also an interesting comparison with the figures, where available, from the reports of Welz and Seeley. The rather general tendency toward an increase reflects the trend for the city as a whole.

TABLE II. CESAREAN SECTION INCIDENCE IN LARGER HOSPITALS (1,000 OR MORE DELIVERIES)

| HOSPITAL CODE NO.* | 1925 (WELZ) | 1930 (SEELEY) | 1945 |
|-----------------------|----------------|------------------|----------------|
| 16 | 1 in 206 | 1 in 203 | 1 in 78 (1.2%) |
| 6 | 1 in 62 | ----- | 1 in 75 (1.3%) |
| 12 | 1 in 142 | 1 in 247 | 1 in 70 (1.4%) |
| 4 | 1 in 73 | 1 in 93 | 1 in 65 (1.5%) |
| 3 | 1 in 471 | 1 in 160 | 1 in 47 (2.1%) |
| 7 | 1 in 97 | 1 in 63 | 1 in 45 (2.1%) |
| 15 | ----- | ----- | 1 in 40 (2.4%) |
| 19 | 1 in 24 | 1 in 74 | 1 in 37 (2.7%) |
| 9 | 1 in 30 | 1 in 32 | 1 in 34 (2.9%) |
| 17 | ----- | ----- | 1 in 34 (2.9%) |
| 8A | ----- | ----- | 1 in 28 (3.5%) |
| 18 | 1 in 34 | 1 in 34 | 1 in 27 (3.7%) |
| 8 | 1 in 31 | 1 in 52 | 1 in 21 (4.6%) |
| 21 | 1 in 206 | 1 in 45 | 1 in 13 (7.4%) |

*Official Code Number, Detroit Department of Health.

In Table III are shown the incidences of the different types of abdominal delivery with their mortality rates where available. The superiority of the low cervical operation over the classical type seems to be rather clearly demonstrated in 1945 as in the previous studies.

TABLE III. TYPES OF CESAREAN SECTION

| | INCIDENCE | MORTALITY | | | |
|-----------------------|-------------|-----------|-------|------|---------|
| | 1945 | 1925 | 1930 | 1945 | |
| Classical | 350 (35.0%) | 13.3% | 7.6% | 6 | (1.71%) |
| Low cervical | 586 (58.9%) | 9.0% | 0.0% | 2 | (0.34%) |
| Cesarean-hysterectomy | 28 (2.8%) | ----- | 9.0% | 0 | |
| Extraperitoneal | 12 (1.2%) | ----- | ----- | 0 | |
| Unknown | 21 (2.1%) | ----- | ----- | 0 | |

In Table IV the hospitals are listed according to the number of deliveries in 1945 as follows: 2,000 or more; 1,000 to 1,999; and less than 1,000. Interesting and, in some instances, significant are the data concerning the general maternal mortality rate, the incidence of cesarean section, and the mortality with abdominal delivery in the different classifications. In the two groups consisting of the larger maternity hospitals the results are quite comparable and are defi-

nitely superior to those of the smaller hospitals. For the latter, however, it should be noted that the maternal mortality would appear as 2.6 per 1,000 live births if Detroit Receiving Hospital (No. 40) were eliminated. This seems justifiable since Receiving has no maternity service, and only extremely ill, or otherwise untransferable, emergency obstetric cases are admitted. Moreover,

TABLE IV. INCIDENCE OF CESAREAN SECTION, GENERAL MATERNAL MORTALITY, AND CESAREAN SECTION MORTALITY ACCORDING TO SIZE OF MATERNITY SERVICE

| HOSPITAL CODE NO. [*] | LIVE BIRTHS | MATERNAL DEATHS | CESAREAN SECTIONS | | |
|---|----------------|--------------------|-------------------|------------|-----------|
| | | | NUMBER | PERCENTAGE | DEATHS |
| A. 2,000 or more births (Maternal death rate: 1.1 per 1,000 live births) | | | | | |
| 8 | 2,021 | 0 | 94 | 4.6 | 0 |
| 9 | 2,274 | 2 | 66 | 2.9 | 0 |
| 21 | 2,953 | 1 | 219 | 7.4 | 1 |
| 16 | 3,130 | 7 | 40 | 1.2 | 1 |
| 15 | 3,619 | 6 | 90 | 2.4 | 0 |
| Total | 13,997 | 16 | 509 | 3.6 | 2 (0.39%) |
| B. 1,000 to 1999 births (Maternal death rate: 1.1 per 1,000 live births) | | | | | |
| 17 | 1,099 | 2 | 32 | 2.9 | 2 |
| 6 | 1,206 | 2 | 16 | 1.3 | 0 |
| 12 | 1,271 | 4 | 18 | 1.4 | 0 |
| 3 | 1,327 | 1 | 28 | 2.1 | 0 |
| 4 | 1,431 | 1 | 22 | 1.5 | 0 |
| 7 | 1,554 | 0 | 34 | 2.1 | 0 |
| 18 | 1,683 | 0 | 61 | 3.6 | 0 |
| 19 | 1,739 | 2 | 47 | 2.7 | 0 |
| 8A | 1,820 | 2 | 65 | 3.5 | 0 |
| Total | 13,130 | 14 | 323 | 2.5 | 2 (0.62%) |
| C. Less than 1,000 births (Maternal death rate: 3.46 per 1,000 live births) | | | | | |
| 35 | 1 | 0 | 0 | 0.0 | 0 |
| 40A | 1 | 0 | 0 | 0.0 | 0 |
| 34 | 12 | 0 | 2 | 16.6 | 0 |
| 38 | 14 | 0 | 0 | 0.0 | 0 |
| 36 | 16 | 0 | 1 | 6.4 | 0 |
| 31 | 20 | 9 | 9 | 45.0 | 0 |
| 40 | 33 | 6 | 0 | 0.0 | 0 |
| 41 | 43 | 0 | 0 | 0.0 | 0 |
| 29 | 60 | 0 | 1 | 1.6 | 0 |
| 37 | 67 | 0 | 0 | 0.0 | 0 |
| 22 | 130 | 1 | 7 | 5.3 | 0 |
| 33 | 161 | 1 | 4 | 2.4 | 0 |
| 25 | 272 | 1 | 2 | 0.7 | 0 |
| 24 | 326 | 1 | 18 | 5.5 | 0 |
| 11 | 329 | 2 | 30 | 9.1 | 0 |
| 23 | 382 | 0 | 6 | 1.6 | 0 |
| 39 | 389 | 2 | 2 | 0.5 | 1 |
| 14 | 420 | 1 | 12 | 2.8 | 1 |
| 20 | 492 | 2 | 5 | 1.0 | 0 |
| 2 | 497 | 1 | 48 | 9.6 | 1 |
| 26 | 552 | 1 | 3 | 0.54 | 0 |
| 5 | 554 | 0 | 5 | 0.9 | 0 |
| 13 | 612 | 1 | 8 | 1.3 | 1 |
| 27 | 712 | 4 | 1 | 0.14 | 0 |
| 1 | 851 | 0 | 4 | 0.47 | 0 |
| Total | 6,946 | 24 | 168 | 2.4 | 4 (2.38%) |
| D. Home deliveries (Maternal death rate: 2.0 per 1000 live births) | | | | | |
| | 2,027 | 4 | 0 | 0.0 | 0 |
| Grand Total | 36,100 | 58 | 1,000 | 2.77 | 8 (0.8%) |

*Official Code Number, Detroit Department of Health.

the large number of serious abortion and ectopic pregnancy cases admitted accounts for deaths which are not truly obstetric but nevertheless (according to Department of Health statistics) are counted in the maternal mortality. On the other hand, we found no defense for the fact that three of the four cesarean fatalities ascribable in whole or in part to questionable indications or treatment occurred in these small hospitals. It is significant to note that only 9 (36 per cent) of the 25 smaller hospitals conformed to the standards of the American College of Surgeons. The importance of proper standards for maternity care is shown by the fact that the mortality rate for cesarean section for all 23 approved hospitals, regardless of their size, was 0.56 per cent for 887 abdominal sections, whereas the death rate for those not approved was 2.65 per cent. In other words, 37.5 per cent of all cesarean deaths for the entire city occurred in the 16 small, substandard institutions where only 11.3 per cent of all cesarean sections and 13.3 per cent of all deliveries took place!

TABLE V. INDICATIONS AS GIVEN FOR CESAREAN SECTIONS IN 1945

| | | | |
|---|-----|-----------------------------------|----|
| Cephalopelvic disproportion | 261 | Malpresentation, malposition | 21 |
| Repeat sections | 166 | Transverse | 5 |
| Hemorrhage | 164 | Brow | 1 |
| Placenta previa | 109 | Face | 3 |
| Abruptio placentae | 55 | Breech | 6 |
| Contracted pelvis | 123 | Transverse arrest | 3 |
| Gen. contracted | 71 | Undefined | 3 |
| Flat | 6 | Fetal indications | 7 |
| Funnel | 13 | "Fetal distress" | 3 |
| Fractured | 1 | Monstrosity | 1 |
| "Subluxation" | 1 | Hydrocephalus | 1 |
| Unclassified | 31 | Triplets + intestinal obstruction | 1 |
| Toxemia | 73 | Prolapsed cord | 1 |
| Eclampsia | 18 | Ruptured uterus | 2 |
| Pre-eclampsia | 15 | Abdominal pregnancy | 1 |
| Nephritic | 3 | Miscellaneous | 51 |
| Hypertensive | 1 | Elderly primipara | 21 |
| Unclassified | 36 | Previous stillbirth | 6 |
| Dystocia | 46 | Diabetes | 5 |
| "Prolonged labor" | 10 | Arrested tuberculosis | 4 |
| Inertia | 14 | Hyperthyroidism + heart disease | 1 |
| Contraction ring | 2 | Psychoneurosis | 1 |
| "Rigid cervix" | 2 | Postpolio, paralysis | 1 |
| "Pelvic dystocia" | 18 | "Spastic condition" | 1 |
| Conditions of perineum, vulva, vagina, cervix, uterus | 30 | "Bleeding tendency" | 1 |
| Previous plastic | 13 | Gangrene mesenteric gland | 1 |
| Previous myomectomy | 2 | "Kidney infection" | 1 |
| Double uterus | 2 | Pulmonary carcinoma | 1 |
| Double vagina | 1 | Rh negative | 4 |
| Stenosis of cervix | 4 | Heart disease | 2 |
| Rectovaginal fistula | 3 | Multiple sclerosis | 1 |
| Atresia, vaginal | 2 | | |
| Prolapse | 1 | | |
| Infected perineum | 1 | | |
| Condylomata | 1 | | |
| Pelvic tumors | 22 | | |
| Uterine fibroids | 16 | | |
| Ovarian cyst | 4 | | |
| Undefined | 2 | | |
| Unknown | | | 33 |
| Charts missing | | 21 | |
| "Ectopic" | | 12 | |
| (2 postmortem cesarean sections not included) | | | |

The indications, as given for the 1,000 sections performed in 1945, are classified in Table V. The validity of the indications could not be subjected to close scrutiny since, in most instances, the data were furnished by the hospitals; and, where data were obtained by us from personal inspection of hospital records, salient features establishing the diagnosis and indications were at times lacking.

Notwithstanding evident extension of indications over former years, to include such new entities as "Rh negative," a comparison of the major reasons for cesarean section with those given in 1925 and 1930 shows less proportional variation than had been anticipated. This comparison is given in Table VI.

TABLE VI

| | 1925 | 1930 | 1945 |
|--|----------|----------|-----------|
| Cephalopelvic disproportion (including contracted pelvis and dystocia) | 48 (31%) | 85 (42%) | 430 (43%) |
| Repeat section | 27 (18%) | 34 (17%) | 166 (17%) |
| Hemorrhage (placenta previa, abruptio) | 17 (11%) | 25 (12%) | 164 (16%) |
| Toxemia | 26 (17%) | 16 (8%) | 73 (7%) |
| All others | 36 (23%) | 43 (21%) | 167 (17%) |

In each of the three series, "cephalopelvic disproportion" (including the various types of "contracted pelvis," whether or not proved by adequate test of labor or pelvimetry) was the most common reason for section, representing 31, 42, and 43 per cent, respectively. The steady increase in frequency of this indication suggests a growing tendency to resort to early section in instances of actual or suspected dystocia. In spite of the growing use of sections, the proportion of cases subjected to "Repeat section" remains at a surprisingly constant level of 18, 17, and 17 per cent, respectively. In 1925, toxemia (including eclampsia, pre-eclampsia, and cardiovascular-renal disease) was the third most frequent indication (17 per cent), whereas in 1930 and 1945 this indication had dropped to fourth place with 8 and 7 per cent each. In 1925 and 1930, hemorrhage (placenta previa and premature placental separation) accounted for 11 and 12 per cent of all sections. In 1945 this indication had risen slightly to 16 per cent of all sections. Miscellaneous reasons comprised 23, 21, and 17 per cent.

While some proportional differences among the major indications for cesarean section are noted since 1925, it is evident that a numerical increase in sections for all causes took place in 1945. Table VII shows a surprising uniformity in the practice of the three hospital groups (classified according to size) with respect to cesarean section for "cephalopelvic disproportion." The greater fre-

TABLE VII. INDICATIONS ACCORDING TO SIZE OF HOSPITALS

| | 2,000 OR MORE BIRTHS | 1,000 TO 1,999 BIRTHS | LESS THAN 1,000 BIRTHS |
|--|-------------------------|--------------------------|---------------------------|
| Cephalopelvic disproportion (including contracted pelvis and dystocia) | 219 (43.0%) | 139 (43.0%) | 73 (43.4%) |
| Repeat section | 98 (19.2%) | 63 (19.5%) | 6 (3.6%) |
| Hemorrhage | 83 (16.3%) | 61 (18.8%) | 21 (12.5%) |
| Toxemia | 28 (5.5%) | 25 (7.7%) | 19 (11.3%) |
| All others | 81 (15.9%) | 35 (10.8%) | 49 (29.2%) |

quency of "Repeat section" in the two larger groups of maternity services suggests that such cases drift to the hands of specialists. On the other hand, the greater proportion of sections for "hemorrhage" in the larger hospitals and the greater percentage of sections for "toxemia" and miscellaneous causes in the smaller ones may indicate some differences in attitude toward the management of these complications.

Most striking in the several contrasting features of the three time periods is the phenomenal reduction in the cesarean death rate. In 1925 there was an appalling maternal mortality of 13 per cent, which in 1930 fell to 4.4, and in 1945 to 0.8 per cent. The 8 maternal deaths of 1945 and their salient clinical features are summarized below:

1. Primipara, white, aged 24 years. . Pregnancy near term complicated by massive edema of the vulva and lower extremities; 30 pound weight gain; hypertension and albuminuria. No improvement after intensive medical treatment in the hospital for seven days. Low servical cesarean section under spinal anesthesia was followed by immediate postoperative shock. Death occurred in one hour and forty-five minutes despite blood transfusion, glucose, plasma, etc. Premature fetus, weighing 3 pounds, 10 ounces, survived. Autopsy: marked anasarca, focal liver necrosis, hemorrhage in abdomen. Cause of death: severe, fulminating pre-eclampsia with postoperative shock.

2. Primipara, white, aged 27 years. Pregnancy at seven months was complicated by headache, dyspnea, edema, albuminuria, and mild phlebitis. There was no improvement under medical management in the hospital during three weeks. Blood pressure rose from 154/90 to 212/140. Low cervical cesarean section under general anesthesia. Premature infant died in twenty-four hours of pulmonary atelectasis. Good postoperative recovery with fall of blood pressure to 134/100. Death from pulmonary embolism on sixteenth day following discharge from hospital. Cause of death: pulmonary embolism.

3. Primipara, white, aged 29 years. Classical cesarean section twenty-four hours after rupture of membranes and prolonged labor associated with unrecognized face presentation. Peritonitis and adynamic ileus evident before operation. Infant weighed 8½ pounds; lived. Death on fifth postoperative day from peritonitis, despite intestinal intubation, penicillin, oxygen, etc. Cause of death: peritonitis.

4. Multipara, Negro, aged 32 years. Entered hospital at term with severe bleeding which continued for twenty-four hours and resulted in shock. Classical cesarean section was performed under general anesthesia while in shock. Death occurred at conclusion of operation. Uterus filled with blood; fetus stillborn. Inadequate preoperative transfusion; 250 c.c. blood, 1,000 c.c. plasma, 500 c.c. glucose given during operation. Cause of death: probable premature separation of the placenta with exsanguination.

5. Primipara, Negro, aged 27 years. Normal pregnancy at term. Hospital chart could not be found. Attending physician stated that "nausea, vomiting and exhaustion" ensued after labor of thirty-six hours. Classical cesarean section was performed under spinal anesthesia. Death occurred on fourth postoperative day. Cause of death unknown.

6. Primipara, white, aged 20 years. Normal pregnancy. Classical cesarean section five hours after admission to hospital with ruptured membranes in active labor. Section indicated by "lack of progress." No evidence of pelvic contraction or disproportion. Infant weighed 7 pounds; lived. Rising postoperative temperature despite penicillin, blood transfusions, etc. Death on tenth postoperative day from peritonitis, septicemia, and wound infection. Autopsy: generalized peritonitis; necrosis of endometrium.

7. Multipara, white, aged 32 years. Classical cesarean section for placenta previa in eighth month, complicated by severe bronchial asthma. Infant stillborn, anencephalic monster.

Death on eighth postoperative day. Autopsy: bronchiectasis, bronchopneumonia, mitral stenosis, pericardial and pleural effusion; chronic adhesive pericarditis.

8. Multipara, white, aged 39 years. Pregnancy at term. Weight 200 pounds. Entered hospital with hypertension 184/120 to 200/116, albuminuria, glycosuria. Fetal heart tones absent. Immediate classical cesarean section under ether anesthesia; cyanosis and fibrillation during operation. Stillborn fetus weighed 10 pounds, 3 ounces. Death on seventh postoperative day ascribed to pulmonary embolus and associated "heart disease, nephritis, and diabetes."

It is evident from a cursory analysis that poor judgment and disregard for indications and contraindications contributed to at least two of the deaths (Cases 3, 4) and that there was questionable justification for cesarean section in two others (Cases 5, 6). It is pertinent to note that six of the eight deaths occurred in hospitals without well-organized obstetric staffs. Assigning the deaths according to the obstetric complication which formed the indication for abdominal delivery, it is evident that toxemia is still the most serious. Among 73 patients sectioned for toxemia, there were three deaths (4.1 per cent). Placenta previa and premature placental separation were associated with two deaths in 164 cases treated by section, although it is evident that in one of these cases (Case 7) cardiac and pulmonary disease were responsible for the fatal outcome. Infection was the final cause of death in two of eight fatalities. No deaths occurred in 166 elective sections performed because of previous section, in 384 ascribed to cephalopelvic disproportion, or in the 46 following dystocia of various types, exclusive of that associated with malpresentation.

Accurate information is not available concerning the causes of fetal deaths, nor of the maternal states responsible for the cesarean sections followed by fetal losses. Of the 78 infant deaths, 28 (35.8 per cent) are known to have been stillborn, and 25 (32.0 per cent) died neonatally. Thirteen (16.6 per cent) were premature. No data are available concerning twelve. Of the stillbirths, three were nonviable monstrosities. Five fetal deaths were attributed to erythroblastosis.

Discussion

This comparative analysis of cesarean section statistics for the City of Detroit during a span of twenty years shows a noteworthy improvement in maternal mortality, as well as a striking change in thought and practice. The steady rise in hospital confinements to a point where, in 1945, less than 6 per cent of obstetric patients were delivered at home indicates an important change in attitude on the part of the public concerning the importance of hospital facilities for childbearing. The fact, moreover, that 75 per cent of deliveries occurred in the larger and, for the most part, better organized maternity services further attests to the better judgment of the majority of patients in seeking good obstetric facilities. This is borne out by the fact that the over-all maternal mortality of these services (1.1 per 1,000 live births) was lower than that of the city as a whole, and only one-third as great as that of the small hospitals which cared for 19.1 per cent of the total births for 1945. As was stated above, 9 of the 25 smaller hospitals conformed to the standards of the American College of Surgeons. Only 13.3 per cent of the total births for the city, or 14 per cent of hospital births occurred in substandard institutions. The mortality rate for home delivery also exceeded that of the larger maternity services.

Incidence.—A survey of the incidence of cesarean section during the twenty years covered in the study shows that this has increased to a point where abdominal delivery is now practically six times more frequent than in 1925, and four times more than in 1930. In the larger hospitals of the 1945 series (com-

prising 75 per cent of all deliveries and 83.2 per cent of all cesarean sections performed), the incidence ranged from 1.2 to a high of 7.4 per cent, the average being 3.0 per cent. In a recent compilation of cesarean section statistics from the literature, Reis and DeCosta³ estimated an average incidence of 3.42 per cent, a figure somewhat higher than the over-all incidence for Detroit of 2.77 per cent in 1945. Reis and De Costa's series includes the results of highly specialized clinics as well as those derived from city and state surveys. Probably a better concept of the over-all picture can be obtained by comparing only community statistics. We have, accordingly, compiled published reports from other cities and states and have arranged them in two groups representing earlier and more recent reports, since it is evident that increasing incidence and lowered mortality are now the universal trend. These statistics are summarized in Tables VIII and IX.

As shown in Tables VIII and IX, the average annual incidence in five separate communities from 1921 to 1936, inclusive, was 1.56 per cent, whereas, from 1937 to 1945, this had increased to 2.84 per cent, a figure which is practically identical with that for Detroit in 1945. The highest incidence of 4.07 per cent in Oakland (and in Los Angeles, as shown in Lazard's report cited by Reis and

TABLE VIII. CESAREAN SECTION INCIDENCE AND MORTALITY DURING YEARS 1921-1936

| AUTHOR | LOCALITY | YEARS | TOTAL BIRTHS | NO. CESAREAN SECTIONS | INCIDENCE PER-CENTAGE | CESAREAN SECTION DEATHS | MORTALITY PER-CENTAGE |
|-----------------------|--------------|---------|--------------|-----------------------|-----------------------|-------------------------|-----------------------|
| Keettel ⁴ | Wisconsin | 1934 | 52,932 | 868 | 1.64 | 28 | 3.23 |
| | | 1935 | 53,794 | 925 | 1.73 | 36 | 3.89 |
| | | 1936 | 53,891 | 1,022 | 1.90 | 33 | 3.23 |
| King ⁵ | New Orleans | 1921-26 | 61,966 | 300 | 0.48 | 47 | 16.1 |
| | | 1927-36 | 92,936 | 1,108 | 1.19 | 64 | 5.9 |
| Williams ⁶ | Philadelphia | 1931 | 33,773 | 601 | 1.8 | 38 | 6.1 |
| | | 1932 | 32,093 | 591 | 1.8 | 36 | 6.0 |
| | | 1933 | 29,228 | 583 | 1.7 | 23 | 3.9 |
| | | 1934 | 29,751 | 638 | 2.1 | 21 | 3.1 |
| | | 1935 | 29,988 | 703 | 2.3 | 32 | 4.6 |
| | | 1936 | 29,652 | 799 | 2.7 | 28 | 3.6 |
| Welz ¹ | Detroit | 1925 | 33,480 | 154 | 0.46 | 20 | 13.0 |
| Seeley ² | Detroit | 1930 | 34,007 | 203 | 0.59 | 9 | 4.43 |
| Average | | | | | 1.56 | | 5.92 |

TABLE IX. CESAREAN SECTION INCIDENCE AND MORTALITY DURING YEARS 1937-1945

| AUTHOR | LOCALITY | YEARS | TOTAL BIRTHS | NO. CESAREAN SECTIONS | INCIDENCE PER-CENTAGE | CESAREAN SECTION DEATHS | MORTALITY PER-CENTAGE |
|---------------------------|----------------|-------|--------------|-----------------------|-----------------------|-------------------------|-----------------------|
| Keettel ⁴ | Wisconsin | 1937 | 55,022 | 1,021 | 1.85 | 35 | 3.43 |
| | | 1938 | 56,213 | 1,233 | 2.19 | 19 | 1.54 |
| | | 1939 | 55,315 | 1,221 | 2.21 | 27 | 2.21 |
| | | 1940 | 56,110 | 1,439 | 2.56 | 32 | 2.22 |
| Williams ⁶ | Philadelphia | 1937 | 30,059 | 811 | 2.7 | 20 | 2.5 |
| | | 1938 | 30,739 | 795 | 2.6 | 13 | 1.6 |
| | | 1939 | 30,232 | 857 | 2.8 | 11 | 1.3 |
| De Normandie ⁷ | Massachusetts | 1937 | 63,988 | 2,082 | 3.2 | 66 | 3.1 |
| | | 1938 | 64,112 | 2,216 | 3.4 | 60 | 2.7 |
| | | 1939 | 64,340 | 1,984 | 3.1 | 54 | 2.7 |
| | | 1940 | 68,261 | 2,312 | 3.4 | 41 | 1.7 |
| | | 1941 | 63,266 | 2,436 | 3.3 | 52 | 2.1 |
| Lees ⁸ | Portland, Ore. | 1942 | 8,547 | 223 | 2.60 | 1 | 0.45 |
| Bell ⁹ | Oakland | 1943 | 7,147 | 290 | 4.07 | 2 | 0.68 |
| ----- | Detroit | 1945 | 36,100 | 1,000 | 2.7 | 8 | 0.80 |
| Average | | | | | 2.84 | | 1.93 |

DeCosta) indicates a much more radical trend in California than in other widely dispersed centers quoted in the literature. The decline in maternal mortality from an average of 5.92 per cent in 1921-1936 to 1.93 per cent in the more recent reports reflects the general trend. The Detroit figure of 0.8 per cent is surpassed only by the smaller series from Portland and Oakland with 0.45 and 0.68 per cent, respectively.

Indications.—With the concomitant increased incidence of cesarean section on the one hand and the lowered mortality on the other, one might well ask whether too many sections are now being performed or whether too few took place in former years. To some extent, both questions can be answered in the affirmative. According to the findings of the Detroit Committee on Maternal Mortality,¹¹ at least 20 of the 58 maternal deaths of 1945 were considered preventable, and many of these might have been avoided by resort to cesarean section. At the same time, the indications for cesarean section were certainly questionable in several of the eight fatal cases in 1945, as cited above. Granted that cesarean section in competent hands and under ideal circumstances has a low surgical mortality, it nevertheless has a comparatively high obstetric risk. Consequently, it is still difficult to justify extremely high cesarean section rates for the usual cross section of private obstetric patients. Ill-defined indications (notably "disproportion" without pelvimetry or adequate trial of labor) suggest an easy escape from potential difficulties for the obstetrician but with serious possibilities for the patient from the immediate surgical hazards and, in future pregnancies, from the dangers of ruptured uterine scar, repeat section, etc.

According to Seeley's report, the primary factor leading to the lowering of the maternal mortality in Detroit from 1925 (Welz) to 1930 was decreased resort to cesarean section in eclampsia. Despite this lesson, there were eighteen sections for eclampsia in 1945, but with no deaths. In 55 other instances where sections were done in the presence of noneconvulsive toxemia there were three deaths. Two of these (Cases 1 and 2) seem to have been treated adequately (one too long, perhaps) by medical means without benefit, and the outcome could be considered as probably unavoidable, unless one should take the extreme view of opposing cesarean section under any circumstance in toxemia. The third patient (Case 8) was subjected to immediate section in the presence of fetal death without any attempt at first improving her serious condition by treatment. However, she survived the operation to die on the seventh day, allegedly of pulmonary embolism.

Disregard of contraindications and overstepping the bounds of prudence were well illustrated, however, in the case of classical section (rather than cesarean-hysterectomy, or better yet, extraperitoneal section or vaginal delivery) in the presence of evident infection after prolonged labor and ruptured membranes associated with an unrecognized face presentation (Case 3). It is noteworthy that cesarean-hysterectomy (28 cases) and extraperitoneal section (12 cases) resulted in no fatalities, presumably under somewhat similar circumstances. Of the two deaths in 164 instances of hemorrhage, one (Case 4) can be criticized on the grounds of sheer neglect for failure to replace blood loss adequately in a patient approaching exitus. The other (Case 7) died as a consequence of pulmonary and cardiac complications and must be considered non-preventable. In two other cases, full information was unobtainable. However, in one (Case 6) it is safe to say that death resulted from infection with little justification for the intervention. Complete details of the other (Case 5) are also lacking, but there is information enough to question seriously the employment of classical cesarean section after thirty-six hours of exhausting

labor. Thus, in four of eight deaths, there are reasons to believe that better judgment and more competent management might have prevented the fatal outcome (or the cesarean section) altogether. In spite of the general improvement in cesarean section mortality, it would appear, then, that with respect to the deaths which did occur the situation has not improved since 1930 when Seeley considered that three of nine cesarean section deaths of his series might have been avoided by better regard for indications and contraindications. One wonders how many more errors were masked by antibiotics, chemotherapy, and the blood bank. Our information did not permit clarification of these points by a thorough study of morbidity, which, as Montgomery stated, is the "Mother of Mortality." However, the analysis of the eight maternal deaths in 1945 quite clearly demonstrates that further substantial improvement in results could have been obtained had indications and contraindications been better observed.

Fetal Results.—It is regrettable that more detailed information concerning the fetal deaths was not available. Although the gross infant mortality in 1945 showed a marked decline over the preceding periods, the fact remains (as pointed out by Aiken¹⁰ and others) that the fetal mortality rate in cesarean section is definitely higher as a whole than for vaginal delivery. The death rate in Detroit during 1945 for all infants under one year of age was 33.6 per thousand live births, whereas 78 infants were lost at birth or neonatally among the 1,000 cesarean sections—more than twice the city rate for the first year of life. The fact that 36 per cent were known to have been stillborn is further reason for questioning the belief that cesarean section offers the best chances for the child. Granting the possibilities in the argument of those favoring cesarean section that the operation is often done for serious conditions which threaten the life of the child as well as the mother (and also well before term) it is evident that the actual effect of abdominal delivery on the fetal welfare can be determined only by careful study of many cesarean sections from the standpoint of the child, as contrasted to results in vaginal delivery under comparable circumstances. Even should such an analysis show fetal advantage in abdominal delivery, there remain certain features unfavorable to the child in cesarean section which offer a major challenge. Aiken and others have discussed the problem of anesthesia, anoxia due to blood loss, and some other factors.

Summary

In Detroit, during 1945, there were 1,000 cesarean sections, or one in 37 births, as contrasted to 154 or one in 217 deliveries in 1925 (Welz), and 203 or one in 167 in 1930 (Seeley). On the other hand, maternal mortality with cesarean section for these series were 13 per cent in 1925, 4.4 per cent in 1930, and only 0.8 per cent in 1945. The fetal death rates for the same years were 11, 12.8, and 7.8 per cent. The incidence of the operation during 1945 in the fourteen larger hospitals with 1,000 or more deliveries varied from one in 78 to one in 13 births, and, in most instances, the 1945 rates represented increases over those for 1925 and 1930, thus reflecting the general trend for the city as a whole. The low cervical operation had become the one most frequently employed by 1945 and, as before, showed distinct maternal advantage over the classical type. Cesarean-hysterectomy and extraperitoneal section were only forty in number but without mortality.

The hospitals were divided into three groups according to numbers of deliveries as follows: 2,000 or more—5 hospitals; 1,000 to 1,999—9 hospitals; and

less than 1,000—25 hospitals. In the first two groups there were 13,997 and 13,130 deliveries with a maternal mortality rate of 1.1 per 1,000 for both. In these same two groups, cesarean sections had incidences of 3.6 and 2.5 per cent, with death rates of 0.39 and 0.62 per cent, respectively. In the third group, there were 6,946 deliveries in the 25 hospitals, with a general maternal mortality of 3.46 per 1,000, and a cesarean section incidence of 2.4 per cent with 2.38 per cent deaths. Moreover, three of the four cesarean fatalities ascribable in whole or in part to questionable treatment occurred in these hospitals.

The number of cesarean sections done for the various indications increased markedly in all important categories. However, the proportional variations remained remarkably constant except for the toxemias of pregnancy. Cesarean sections for these conditions had increased from 26 in 1925 to 73 in 1945, but these figures represented a decrease from 17 per cent of all sections in 1925 down to 7 per cent in 1945. The proportional and absolute increase under the heading "Miscellaneous" is explained in part by some new indications such as "Rh negative."

An outstanding feature, on comparing the three periods, is the marked reduction in cesarean section mortality—from the appalling rate of 13 per cent in 1925, to 4.4 in 1930, and down to only 8 cases or 0.8 per cent in 1945. In spite of this good record for 1945, there was, however, good reason to believe, on the basis of the available data, that poor judgment and disregard of indications and contraindications were largely responsible for two of the eight deaths. In at least two others, the indications for abdominal delivery were highly questionable. Regarding the conditions for which cesarean section was done, the toxemias remain the most serious—three deaths in 73 during 1945. There were also two fatalities among the 164 operations for placenta previa and premature separation of the placenta. No deaths occurred in 166 elective sections performed because of previous cesarean, and none in the 384 done for cephalopelvic disproportion.

Only a few details were secured regarding the fetal deaths. Of the 78 infants lost, 28 (35.8 per cent) are known to have been stillborn, and 25 (32 per cent) were neonatal deaths. At least 13, or 16.6 per cent, were premature infants. Three were maldeveloped, and five deaths were attributed to erythroblastosis.

This analysis of cesarean sections from Detroit led to some interesting conclusions, comparisons with other communities, and other data as follows: A rise in hospital confinements during the twenty years to more than 94 per cent of the deliveries in 1945 was accompanied by a reduction in the general maternal mortality to 1.6 per 1,000 live births. At the same time, there was an increase in cesarean sections from 154 in 1925 to 1,000 in 1945, a percentage of 2.7, or one in 37 births. This high incidence is in accord with the average (2.84 per cent) obtained from the recent studies in various states and cities. The Detroit cesarean section mortality rate of 0.8 per cent compared very favorably with that of these other communities. In Detroit's largest and, generally speaking, better organized obstetric services, there were 75 per cent of the city's deliveries

with a substantially lower over-all mortality. In these hospitals there was also a definitely higher incidence of cesarean section, but again a very low death rate (0.48 per cent). In view of the markedly increased incidence of cesarean sections on the one hand and the greatly decreased mortality on the other, it is well to ask if too many are now being done or if too few were done before. There is evidence that, in 1945, many sections were done for scant reason, to say the least. Apparently there is widespread disregard of the fact that, though the death rate is low, surgically speaking, it represents a high immediate obstetric risk, as well as a definite hazard for future pregnancies. On the other side of the question, it is noteworthy that in 1945 at least 20 of the 58 maternal deaths were considered to have been preventable, a number of them by timely cesarean section. Both sides of the question, then, seem to involve a proper regard for established indications and contraindications. Specifically pointing the way to further improvement, as mentioned before, is the fact that, in at least four of the eight cesarean deaths in 1945, the fatal outcome was in considerable part due to faulty judgment or management.

The fetal mortality rate of 7.8 per cent in the 1945 cesarean sections, though definitely better than in previous years, is still twice the over-all death rate for infants during the first year of life. The fact that 36 per cent were stillborn again emphasizes the fact that cesarean section does not necessarily offer the best chances for a living child. Hence, there is no justification for undue extension of the use of cesarean section for purely fetal indications.

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Discussion

DR. EDWIN J. DECOSTA, Chicago.—Detroit is to be congratulated for its exceedingly low maternal death rate and low cesarean section death rate.

For the sake of the record, it seems desirable at this time to compare briefly the Detroit figures with those of Chicago. During 1945, Chicago hospital deliveries, which constitute some 95 per cent of the total deliveries, numbered 59,343, of which 2,177 were cesarean section, a rate of 3.67 per cent. The maternal death rate for the entire group was 1.62 per thousand, for cesarean section 6.4. During the same period, out of the total of 125,016 deliveries in the state of Illinois, the cesarean section incidence was 3.6 per cent.

Dr. Siddall has surveyed 690,000 deliveries in various communities and has concluded that the average community incidence of cesarean section is 2.84 per cent. In a recent publication with Dr. Reis, we estimated this over-all incidence to be 3.42 per cent. According to the state of Illinois, we have been a bit conservative; according to Detroit, a bit radical. It is interesting to note that out of some 45,800 deliveries mentioned by Drs. Tollefson and Krahulik in their discussion of our paper, the incidence of cesarean section in Los Angeles private hospitals was 9.2 per cent, while in Los Angeles County Hospital

it was 3.32 per cent. I mention these variations only to point out that one can reach almost any conclusion depending upon the number of cases reviewed and the area from which the material is gathered.

We all appreciate that the risk of cesarean section is many times greater than the risk of vaginal delivery. Yet hundreds of consecutive cases of cesarean section have been performed in our larger hospitals without a single death. In our own series, this numbered 822 through 1946. But we must not convey to the public the thought that women may be delivered as safely abdominally as vaginally. The records of Detroit and Chicago prove otherwise, and these are most enviable records.

Drs. Mack and Siddall have not stated the source of their figures. I assume that they were provided by the Detroit Department of Health. Unless one has worked with statistics, it is difficult to appreciate the tremendous problems involved in gathering accurate figures concerning the maternal death rate. In a country like ours, where every move from cradle to grave is free and unrecorded, accurate information can be obtained only with great pains.

Comparative studies, such as we have just had the privilege of hearing, are most important in the evaluation of progress and in restraining unbridled surgery. By this method we learn whether or not our efforts are worth while.

DR. GEORGE KAMPERMAN, Detroit, Mich.—In noting the change and improvement in the maternal mortality statistics, it is interesting to consider the factors contributing to this improvement. In the first series reported, we are considering the period when most of the cesarean sections were performed by the general surgeon. It took a long time for obstetrics to gain recognition as a specialty. And the family practitioner, who at first felt the obstetrician was an intruder, much preferred to call on a general surgeon for his sections. The general surgeon was not a true consultant in those instances but was merely a technician who performed the operation on the say-so of the family practitioner. No matter how skillfully the operator had performed, the results were bad, not so much perhaps due to the indications but more because of the contraindications, which were ignored or not considered. From the standpoint of maternal mortality, contraindications are more important even than indications. And the family practitioner in many cases was not cognizant of the fact that he himself was establishing the contraindications. He had not then learned that a first stage of labor can be so conducted that contraindications are practically nonexistent, in case a cesarean section were eventually found indicated. I believe it is the consciousness of contraindications that has been the largest factor in the reduction of maternal mortality. We have learned when *not* to perform a cesarean section.

Another factor has been the recognition that a patient in the acute eclamptic convulsive state is a poor risk for major operations. It also clouded the statistics in that, doubtless, many deaths due to eclampsia were attributed to cesarean section. The conservative treatment of eclampsia has been a factor in reducing the death list from cesarean section.

It will be noted that the incidence of cesarean section shows an increasing frequency. This, no doubt, is due, to a great extent, to the widening of the indications. Obstetrics has become more and more a surgical specialty. Well-trained obstetricians have at their command surgical procedures not possessed by the family practitioner. He, by training, can do certain things for his patient, and he argues that if he can do certain things safely for his patient, why should not his patient have the benefit of his training. As a result, no doubt, many cases are sectioned simply because the labor promises to be very difficult.

This means that obstetric practice is coming to a new cross road. Cesarean section is now becoming so safe an operation that the obstetrician, often on the insistence of the patient, is induced to perform a section rather than let the patient have a normal, although difficult, delivery.

I am glad the essayist calls attention to the fact that although cesarean section is becoming a safer operation, vaginal delivery, in the majority of cases, is still the safer procedure. Obstetricians should stop, look, and listen, to make sure that cesarean section, so valuable a procedure, is indicated and is not abused so that it may become a menace to our patients.

DR. E. L. KING, New Orleans, La.—We conducted a study in 1926 for the previous six years and again in 1930 for a ten-year period. From 1921 to 1926 there were a little over 61,000 births in our city. One-fourth of these were delivered in hospitals. There were 300 cesarean sections performed, a ratio of 1:206. In the second series, there were 92,900 deliveries with about 60 per cent delivered in hospitals, 1,108 cesarean sections were performed, or a ratio of 1:84. During the past five years, 74,810 deliveries have occurred in New Orleans, approximately 71,000 being delivered in hospitals, or 96 per cent hospital deliveries in the past five years, with 2,720 cesarean sections, a ratio of 1:28.

In the first series, there was 15 per cent maternal mortality. In the second series, 64 of the 1,108 cesarean section patients died, a percentage of 5.9. Of the 2,720 cesarean sections in the last five-year period, there were thirty-three deaths, or 1.21 per cent.

In the first series, there was a fetal mortality rate of 18 per cent, but it should be remembered that this includes statistics from Charity Hospital where there were many complicated cases.

DR. RUDOLPH HOLMES, Charlottesville, Va.—I had the misfortune of beginning practice when there was only one indication for section and that was gross disproportion.

I think craniotomy still has its place in obstetrics. Within the range of indications for it, craniotomy is the safest operation a parturient may have, and it is the wise procedure to follow when the infant is a monster, living or dead. I think that cesarean section is being done too often. The smaller the hospital, the higher the incidence of cesarean section and the higher the incidence of death. In Illinois the highest incidence of cesarean section was in the smallest country hospitals. That is not right.

DR. MACK (Closing).—It is very gratifying to learn of the downward trend in cesarean section mortality in other communities, as has been brought out in the discussion. One purpose of this study was to show that community figures give a better over-all picture of the operation than is derived from statistics of individual hospitals or clinics. The public gains a false sense of security from hospital reports with high incidence and low mortality. As Dr. King pointed out, bad results are still obtained, to a large extent in substandard hospitals, where the indications and contraindications are not properly heeded. We believe that even with modern facilities no one should dare to take undue liberty with indications or contraindications.

SERUM BETA-GLUCURONIDASE LEVELS DURING TOXEMIA OF PREGNANCY*

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FOR some time science has sought a specific chemical or biologic fraction or reaction, the presence, absence, or concentration of which would identify the toxemias of pregnancy. To be ideal, such a test should probably possess several characteristics; it should be specific for that syndrome, it should warn the obstetrician of an impending toxemia, it should distinguish pre-eclampsia from essential hypertension, it should be of prognostic value, and the method of analysis should be relatively easy and accurate. In general, attempts in this direction have been along chemical, biologic, hormonal, or enzymatic lines. In regard to the first three of these, studies have been largely concerned with the blood uric acid level,¹ the uric acid clearance,²⁻⁴ reaction to pituitrin⁵ and cold pressor tests,⁶ serum estrogen^{7, 8} and gonadotropin levels,⁹ and urinary pregnandiol excretion.^{10, 11}

Pregnancy and toxemia of pregnancy cause many metabolic changes which may be manifested in alterations of the enzyme structure of the organism.

Abderhalden¹² noted that serum from pregnant women, incubated with placental tissue in a dialyzing tube, liberated amino acids which could be identified in the dialysate. This reaction became the basis for a pregnancy test. Dieckmann¹³ found the Abderhalden negative in some eclamptic patients. Obata¹⁴ found normal and eclamptic blood serum and placental extract lethal for white mice in equivalents; serum from normally pregnant patients, however, incubated with placental extract, inactivated placental toxin, whereas eclamptic serum did not. Obata believed the reaction an antigen-antibody one. Hayashi¹⁵ discovered that the detoxification effect was destroyed at room temperature in four to five days, or upon heating to 50 to 60 degrees for one-half hour, thereby suggesting its enzymatic nature. Dieckmann,¹⁶ using mice, confirmed Obata's results and devised a different method based on the clotting mechanism (employing the technique of Loch and co-workers¹⁷) for testing the neutralizing substances. Clotting of the plasma was delayed if serum was obtained from eclamptic patients. Dieckmann concluded that there was no specific placental toxin since extracts of beef lung gave the same response. Recently, Schneider^{18, 19} has revived these experiments and has identified the placental toxin as thromboplastin.²⁰

Von Fekete,²¹ using a bioassay employing guinea pig intestine strip, found pregnancy serum would inactivate the oxytocic factor in solution posterior pituitary, the basis of Page's²² pitocinase test for pregnancy. Aragon²³ tested

*Read before the Central Association of Obstetricians and Gynecologists, Oct. 25, 1917, Louisville, Ky.

serum from normally pregnant and toxemic patients, using Page's method, and found a progressive increase in pitocinase during normal pregnancy. Values for toxemic patients, however, were scattered on either side of the normal curve and consequently were of no diagnostic or prognostic value.

Smith and Smith²⁴ reported an increased fibrinolytic activity of the blood serum during pre-eclampsia, less in hypertensive patients with superimposed pregnancy. Willson and Munnell,²⁵ however, were unable to use it for accurately differentiating between "vascular renal disease and the specific pregnancy toxemias." Moreover, fibrinolysis tended to be increased in those patients exhibiting proteinuria irrespective of the type of toxemia studied. And fibrinolysins are found in many nonpregnant conditions.

Among other reports are these: Histaminase²⁶ (bio-assay) increases five hundredfold to a thousandfold during pregnancy and may be employed as a prognostic guide in abortions. Contradictory reports exist concerning this enzyme during toxemia of pregnancy, it being lowered according to some^{27, 28} and normal according to another.²⁹ Renin³⁰ is increased during eclampsia. Plasma lipase³¹ falls during pregnancy, whereas blood amylase³² is more active. Angiotonase³³ increases four- to tenfold during the second half of normal pregnancy, but values from toxemic patients are not significantly altered. Serum cholinesterase³⁴ is lower during normal pregnancy.

We³⁵ have previously reported on the serum beta-glucuronidase activity during normal and toxemic pregnancy and upon certain organ tissues. We found the mean curve during normal pregnancy to increase from 3 μ g at three months to 13.5 near term. Values during pre-eclampsia were higher, usually above 20, whereas those for hypertensive toxemia were within the normal range. We postulated that beta-glucuronidase levels might be employed to differentiate pre-eclampsia from hypertensive toxemia of pregnancy. An analysis of various tissues failed to suggest the site of formation of the enzyme.

The purposes of this report are (1) to re-emphasize the differentiation by serum beta-glucuronidase values of pre-eclampsia and hypertensive toxemia of pregnancy; (2) to illustrate the use of beta-glucuronidase levels in detecting a potential pre-eclampsia; (3) to point out that beta-glucuronidase values are apparently of no prognostic value; (4) to report levels for convulsive toxemia of pregnancy; (5) to illustrate examples of toxemia of pregnancy in which repeated serum levels of enzyme were obtained and to correlate these with the clinical course of the disease.

Materials and Method

A total of 118 patients were studied. These consisted of seventy-nine with toxemia of pregnancy and forty-five with excessive weight gain. Some of the latter developed a toxemia. In addition, there was one patient with a functional amenorrhea and superimposed pregnancy and another with uremia.

The method of analysis was that described by Tallalay, Fishman, and Huggins.³⁶

Basis of Diagnosis.—According to established recommendations, the toxemias of pregnancy may be classified as follows: (1) conditions peculiar to pregnancy such as (a) pre-eclampsia and (b) eclampsia and coma; (2) conditions not peculiar to pregnancy, including essential hypertension, malignant hypertension, acute and chronic nephritis, and pyelonephritis. In this study

we have considered nonconvulsive patients as being either pre-eclamptic or hypertensive, since no known cases of nephritis, malignant hypertension, or pyelonephritis were observed. In addition, we have grouped cases of recurrent toxemia with the hypertensive patients.

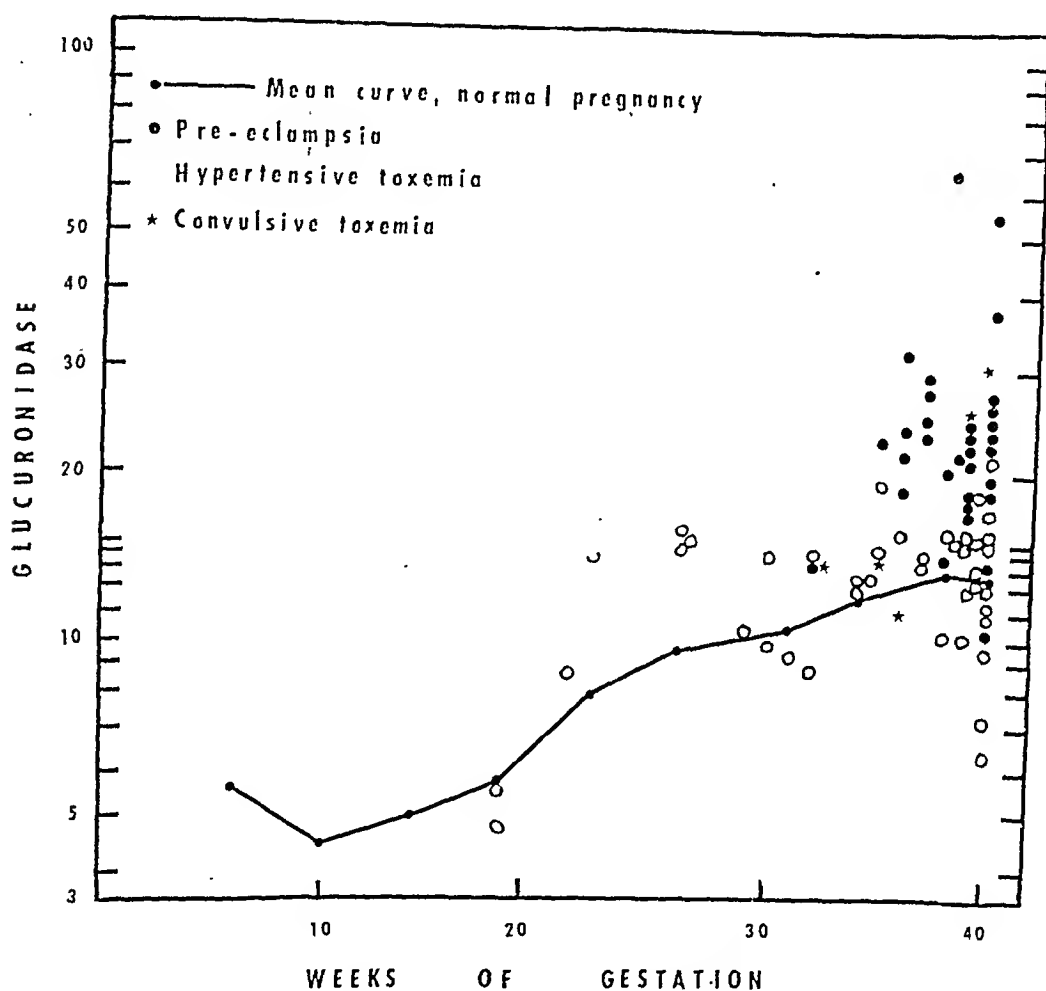


Fig. 1.—Serum glucuronidase. Toxemia of pregnancy (semi-log scale).

Certain clinical characteristics have become associated with pre-eclampsia and hypertensive toxemia, among which may be mentioned the following: Age distribution is higher in hypertensive toxemia than in pre-eclampsia. Multigravidity is more characteristic of hypertensive patients. Too rapid weight gain (edema) is mostly found during pre-eclampsia. Averages for systolic and diastolic blood pressure are lower during severe pre-eclampsia than during severe hypertensive toxemia. The onset of toxemia is earlier in the latter group and its duration more prolonged post partum. And hypertensive patients more often possess a family background for vascular disease. The data in Table I compare favorably with that reported by Dieckmann.¹³

Using these criteria, thirty-three patients were judged to have pre-eclampsia; five, eclampsia*; and forty-two, hypertensive toxemia of pregnancy. Inasmuch as some of those believed to have mild hypertensive toxemia were

*One pre-eclamptic patient under observation subsequently developed eclampsia.

primigravidas, a subsequent follow-up through successive pregnancies will be necessary to establish conclusively that they suffer from early hypertensive vascular disease.

H.G. 383214 - PRE-ECLAMPSIA-GLUCURONIDASE

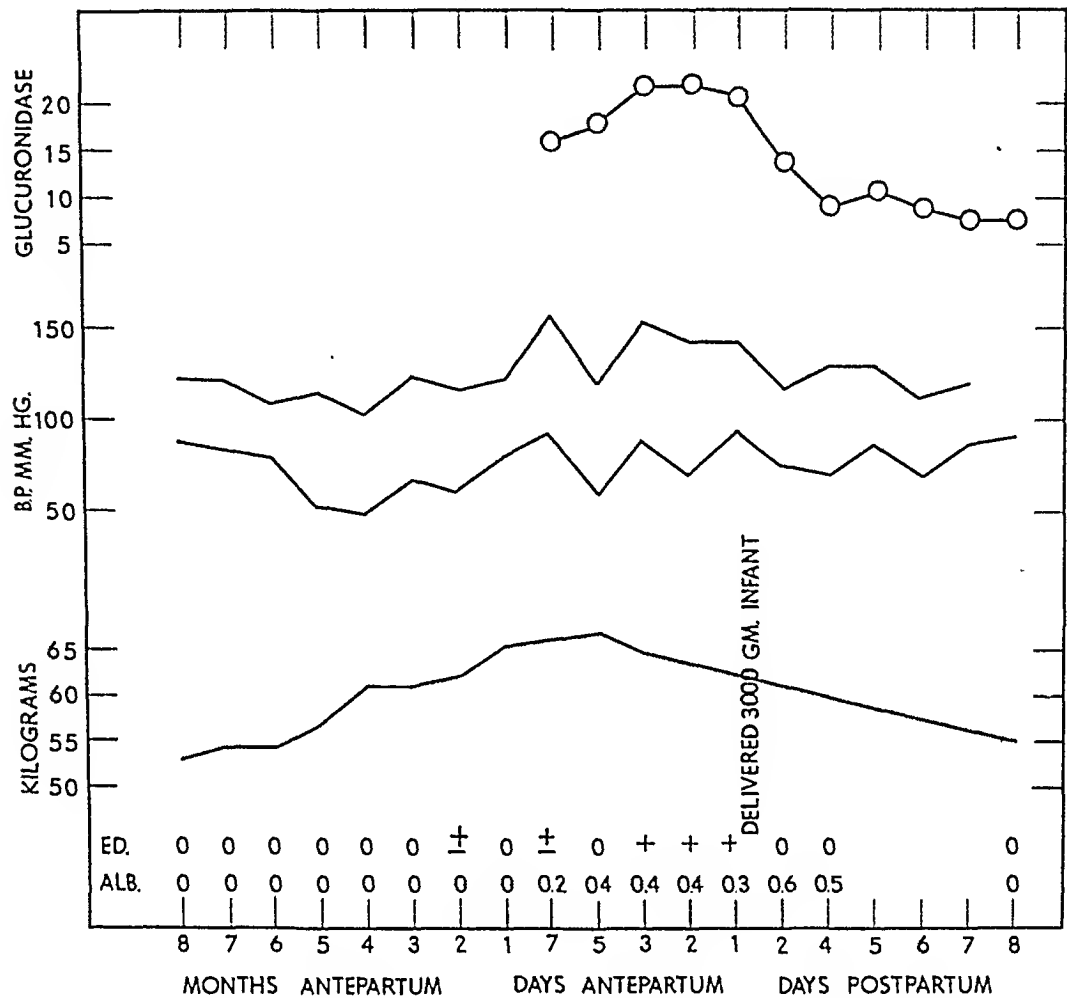


Fig. 2.—H. G. (383214). Age, 23 years, para, 0, gravida, 1; due March 4, 1947; delivered Feb. 13, 1947. Pre-eclampsia. Glucuronidase reported as micrograms per cubic centimeter.

Pre-eclampsia.—Although the upper range for normal pregnancy does not exceed 17.5 μg per cubic centimeter at term,³⁵ with few exceptions serum beta-glucuronidase values were high during pre-eclampsia. In fact, a figure above 20 μg seemed diagnostic for this condition. Some unusually high values were encountered (Fig. 1). Figs. 2 and 3 are composite graphs for pre-eclamptic patients. Serum beta-glucuronidase levels tended to remain elevated during some of the duration of the disease. Our experience failed to attach much prognostic value to the test after the syndrome appeared. In one pre-eclamptic patient a relatively normal value (13.4 μg) was encountered just previous to delivery, but this patient experienced an eclamptic seizure seventeen hours post partum. In another (Fig. 2) the proteinuria and blood pressure and edema increased steadily without a progressive elevation of the enzyme. In fact, the concentration tended to rise toward a plateau, both before and during the disease, and then in some instances to fall to even normal levels, although the syn-

drome still persisted (Figs. 2 and 3). During the puerperium the concentration fell rapidly, except for slight rises on the fourth to sixth days, possibly due to changes in hormone metabolism or perhaps the result of a mild endometritis.

D P 347493-PREECLAMPSIA GLUCURONIDASE

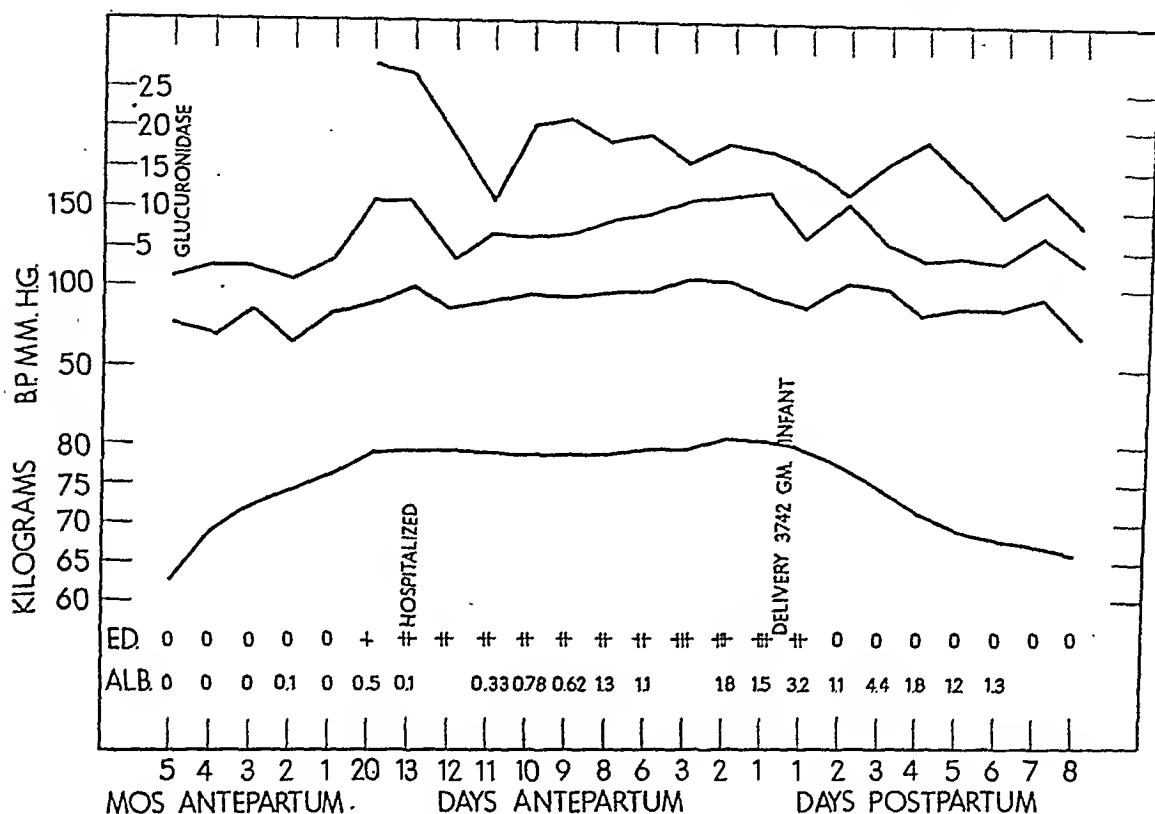


Fig. 3.—O. P. (347493). Age, 30 years, para, 0, gravida, 1; due Jan. 30, 1947; delivered Feb. 9, 1947. Pre-eclampsia. Glucuronidase reported as micrograms per cubic centimeter.

Hypertensive Toxemia.—Most levels were within the range for normal pregnancy. Several patients were observed as long as five months without an elevation of serum beta-glucuronidase, one of which is portrayed graphically (Fig. 4). It will be noted that this patient, and the one whose levels are shown in Fig. 5, exhibited considerable proteinuria without an elevation of enzyme concentration in the serum.

Convulsive Toxemia.—Five patients were observed who had convulsions. Case histories are as follows:

CASE 1.—F. S.,* para 0, gravida i, aged 15 years, due July 2, 1947, was first observed on Dec. 16, 1946, with a normal blood pressure and no edema or proteinuria. The subsequent prenatal course was uneventful except for a weight gain of 2 kilograms between April 21 and May 5 and headache on this last visit. On June 1, 1947, labor commenced spontaneously and the patient was delivered spontaneously of a living female infant weighing 3,600 grams. At that time the blood pressure was 140/110, edema 1 plus, and urine negative for protein. Three hours later one convulsion occurred; blood pressure was 144/100 and urine 1 plus pro-

*Patient from another hospital

teinuria. Subsequently, however, the blood pressure and urine returned rapidly to normal. The puerperium was uncomplicated. The serum beta-glucuronidase level at the time of convulsive seizure was 25.2 μ g per cubic centimeter.

CASE 2.—M. G.,* para 0, gravida i, aged 18 years, due Feb. 27, 1947, was first observed on Feb. 4, 1947, with a normal blood pressure, 2 plus edema, and normal urine. On February 12 the patient experienced headache and scotomas, followed by six convulsions. Examination at that time disclosed a blood pressure of 170/120, 2 plus edema, and 2 plus proteinuria. Following premature artificial rupture of the membranes, labor commenced spontaneously and the patient was delivered by low forceps of a living female infant weighing 3,000 grams. Blood pressure and urine returned rapidly to normal during the puerperium. The serum beta-glucuronidase level at the time of convulsive seizures was 30 μ g per cubic centimeter and subsequent levels were 27, 25, 32, 20, 19, 19, and 7 μ g during the succeeding several days.

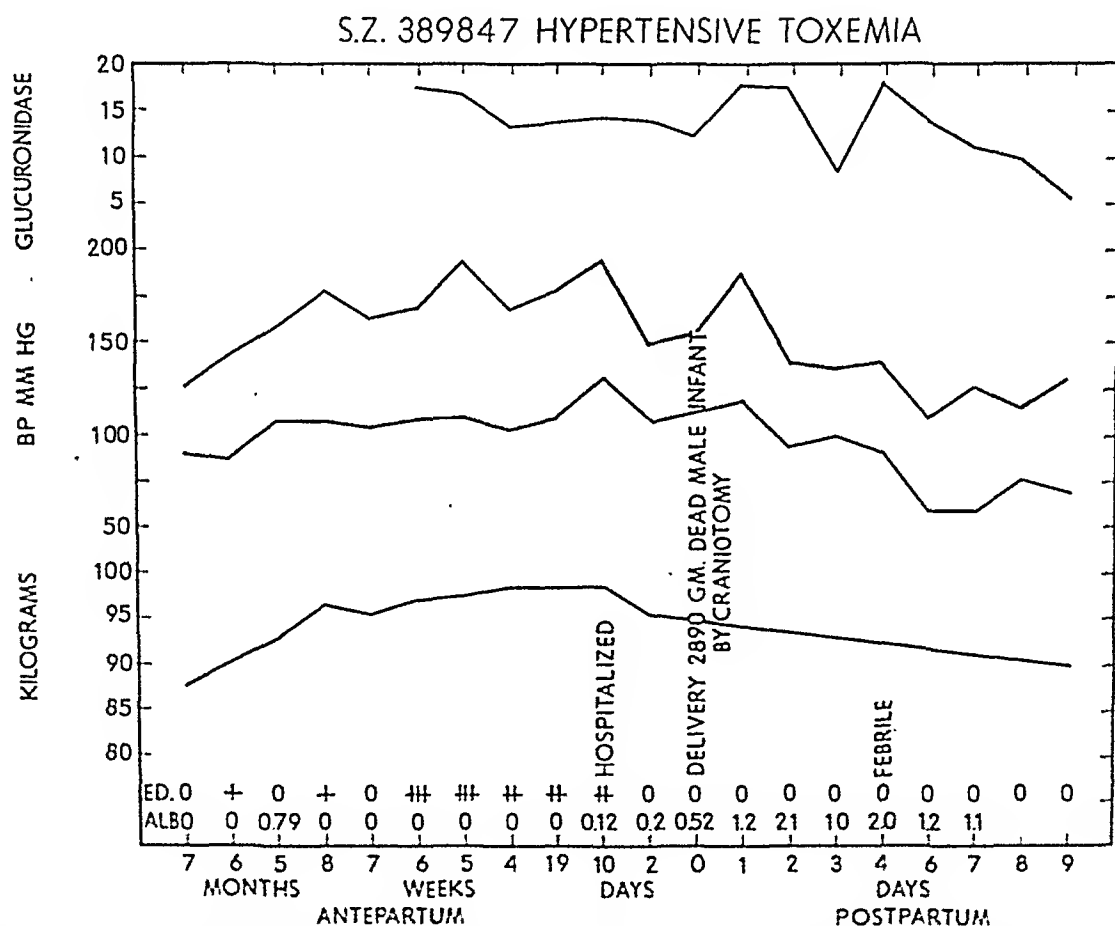


Fig. 4.—S. Z. (389847). Age, 32 years; para, 0, gravida, i; due March 22, 1947, delivered March 17, 1947. Hypertensive toxemia. Glucuronidase reported as micrograms per cubic centimeter.

CASE 3.—M. K., No. 403354, para 0, gravida i, aged 19 years, due May 14, 1947, was first observed on March 19, 1947, with headache, blurring of vision, blood pressure 160/114, 3 plus edema, and 4 plus proteinuria. Labor commenced spontaneously on that date and the patient was delivered of a living female infant weighing 1,190 grams by low forceps operation. Seventeen hours later one convulsion occurred, followed by a short period of coma. The subsequent puerperium was uncomplicated. Blood pressure on discharge was

*Patient from another hospital.

140/90 and urine negative for protein. The serum beta-glucuronidase level at the time of delivery was 13.4 μ g per cubic centimeter, only slightly above the average for normal pregnancy at the age of gestation. No subsequent levels were obtained.

CASE 4.—J. G.,* para 0, gravida i, aged 17 years, due June 26, 1947, was first observed on May 1, 1947, with a history of a weight gain of seventy-three pounds, headache, dizziness, vomiting, and blurring of vision. Examination disclosed a blood pressure of 210/150, 4 plus edema, and proteinuria. One convulsion occurred on May 2, 1947, followed by two days of coma. The blood pressure, during this period, fluctuated between 240 and 160 systolic and 150 and 102 diastolic. The patient was considered moribund on several occasions. A living female infant weighing 1,700 grams was delivered by cesarean section on May 3, 1947. During the twenty-five days of postpartum hospitalization all edema disappeared, the blood pressure gradually fell to 150/100, but the proteinuria persisted. Serum glucuronidase levels were 11.8 μ g per cubic centimeter on May 2, 1947, the day of convulsion, and 5.8, 6.4, 5.8, and 9.8 μ g during the succeeding four days. The urea clearance test was 30 per cent of normal at the time of discharge from the hospital.

CASE 5.—M. T., No. 320650, para 2, gravida iii, aged 40 years, due April 15, 1947, was first seen on March 14, 1947, in coma of four hours' duration. Previous to its onset, the patient had complained of severe headache and vomiting. There was a five-year history of hypertension. Examination disclosed blood pressure of 200/110, pulse 120/minute, 4 plus proteinuria, and slight edema. One convulsion occurred three hours after admission. Membranes were ruptured artificially, labor commenced immediately, and the patient was delivered by low forceps of a living female infant weighing 1,855 grams. This case is portrayed graphically in Fig. 5.

It is believed the first three are illustrative of typical eclampsia. Note the rapid onset and rapid disappearance of hypertension, edema, and proteinuria incident to recovery. The fourth patient exhibited blood pressures above 200 mm. systolic, had more persistent hypertension and proteinuria post partum, and had a reduced urea clearance rate on discharge. And the last patient had evidence of residual vascular damage following the experience. It is doubtful if this last case was true eclampsia, being more probably hypertensive encephalopathy.

TABLE I. SUMMARY OF CLINICAL DATA

| | PRE-ECLAMPTIC | HYPERTENSIVE | ECLAMPTIC |
|---|---------------|--------------|-----------|
| Total patients | 33 | 42 | 5 |
| Average age | 25 | 29 | 25 |
| Per cent primiparas | 71 | 47 | 80 |
| Per cent > gain of 12 kilograms | 66 | 19 | 60 |
| Per cent > 180 B.P. | 6 | 30 | 60 |
| Per cent > 1.5 Gm./24 hr. of protein | 50 | 19 | 60 |
| Per cent onset < 34 weeks | 13 | 65 | 60 |
| Per cent family history of hypertension | 37 | 70 | 20 |

From these results it is obvious that serum beta-glucuronidase levels are not elevated during all cases of convulsive toxemia of pregnancy.

Abnormal weight gain.—At the Lying-in Hospital patients exhibiting an abnormal weight gain during pregnancy† are followed in the toxemic clinic. The caloric intake in such patients is evaluated by a dietician.‡ If the rapid weight gain persists, particularly after twenty-eight weeks, or if edema appears,

*Patient from another hospital.

†More than an average of 0.6 kilograms per week.

‡The normal prenatal diet consists of: 1,747 calories, 85 Gm. of protein, 181 Gm. of COOH, and 76 Gm. of fat.

a pre-eclamptic diet* is recommended. In this study forty-five such patients were selected at random after twenty-eight weeks of pregnancy and from one to four serum beta-glucuronidase levels obtained every one, two, or three weeks. In none of these had edema, hypertension, or proteinuria as yet appeared. Of this group, thirteen eventually developed two or more of the cardinal signs of toxemia: edema, proteinuria, and hypertension. Of these, six were judged to have pre-eclampsia. Of those who did not develop toxemia, two had had a previous toxemia, presumably a pre-eclampsia. Fig. 6 illustrates the findings. Note the consistently higher values in cases developing pre-eclampsia. One of these (Case 15, Fig. 6) was observed for eight weeks previous to the onset of

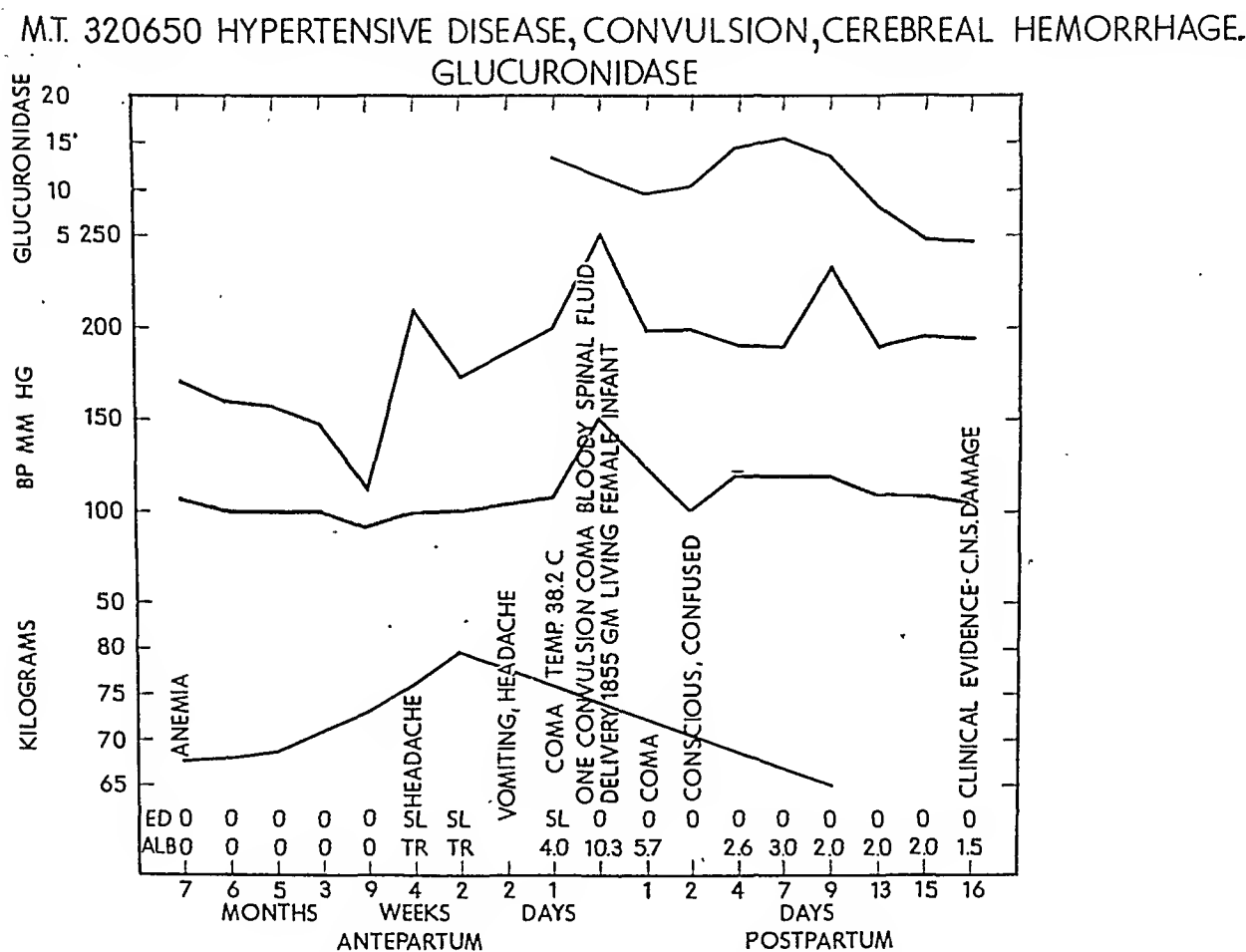


Fig. 5.—M. T. (320650). Age, 40 years, para, 2, gravida, iii; due April 15, 1947; delivered March 14, 1947. Hypertensive disease, convulsion, and cerebral hemorrhage. Glucuronidase reported as micrograms per cubic centimeter.

the syndrome. Note also that most values are in excess of the mean curve for normal pregnancy, suggesting that beta-glucuronidase levels are closely allied to water retention. Inasmuch as these patients were treated for potential pre-eclampsia, and received dietary advice, it is reasonable to suppose that their medical and obstetric management may have averted other cases. Of those patients who developed a toxemia but did not have pre-eclampsia, two had recurrent toxemia. The remainder (five patients) had a slight hypertension

*The pre-eclamptic diet is the same as the normal diet but contains less than 3.0 Gm. of NaCl per day.

during labor (less than 160 systolic), without a proteinuria and with little edema. According to past experience at this clinic many such cases represent early manifestations of hypertensive vascular disease.

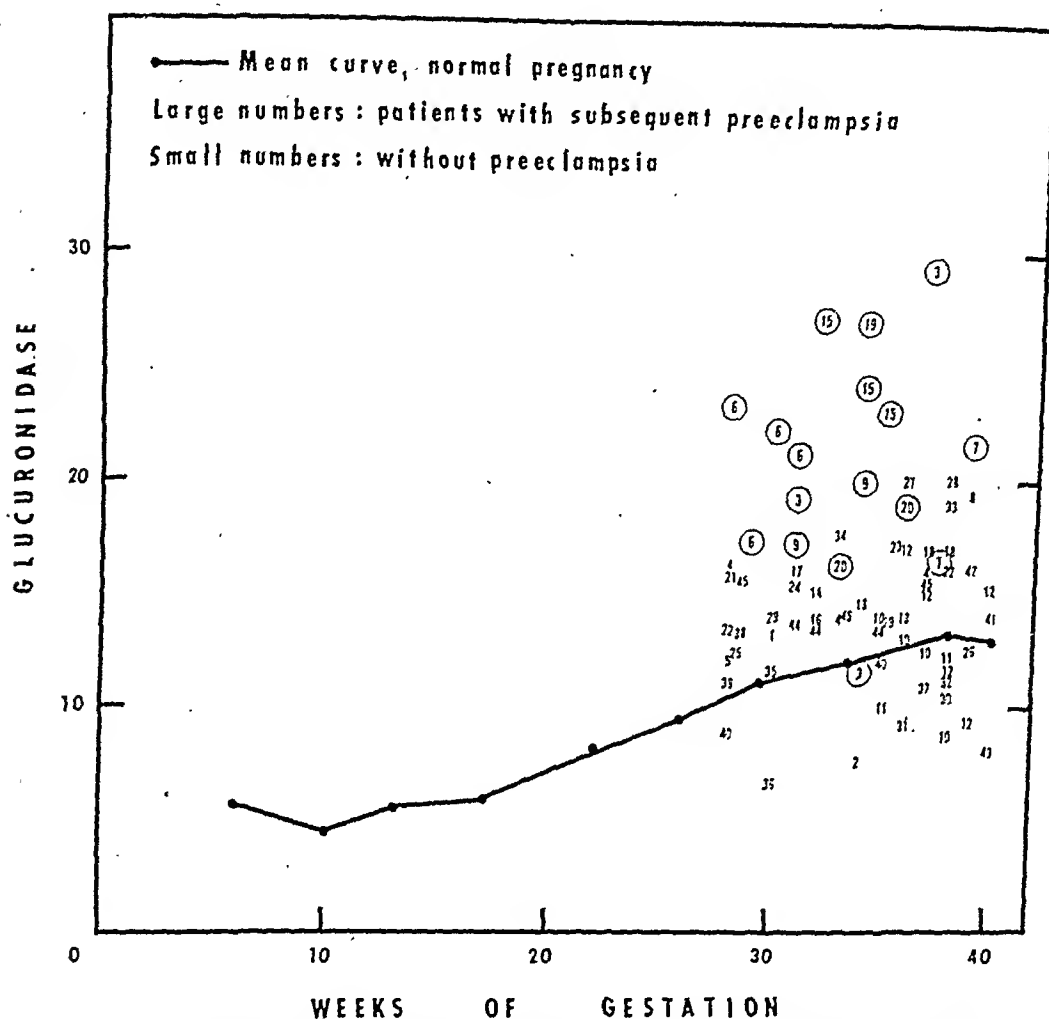


Fig. 6.—Serum glucuronidase. Excessive weight gain in forty-five patients.

Comment

The biologic characteristics of beta-glucuronidase have been studied by Fishman³⁷⁻⁴⁰ and by Fishman and Fishman.⁴¹ Fishman found an increase of enzyme activity in the vital organs (liver, spleen, and kidney) of animals fed nonestrogenic glucuronogenic substances, whereas ovariectomized mice on estrogens show a 100 per cent elevation in uterine beta-glucuronidase without an increase in liver concentration. The enzyme, then, is responsible for the conjugation of estrogens in the uterus.⁴² In addition, beta-glucuronidase is concerned with the liberation of pregnandiol since the latter is excreted as a glucuronide ester, and it is involved in the detoxification of hydrocarbon poisons⁴³ as well as in the metabolism of many other substances.

Although no figures are available for uterine estrogens during preeclampsia, it is known that their placental and serum concentration⁹ is low during that disease, as is the urinary excretion of pregnandiol.^{10, 11} The high

serum concentration of beta-glucuronidase during pre-eclampsia in the presence of a low serum, urine, and tissue substrate (estrogens and progesterone products) would seem puzzling but may be explained in the metabolism of the latter.

As yet the intermediary metabolism of steroids is incompletely understood. Progesterone, administered parenterally, cannot be entirely accounted for as urinary pregnandiol during pregnancy.⁴⁴ So the latter apparently represents only a fraction of the end product of progesterone. The intermediary phases of estrogen metabolism are similarly obscure. If such is the case the serum elevation of beta-glucuronidase during pre-eclampsia merely reflects some unknown disturbance in the metabolism of sex hormones.

In support of this are the following facts: During pregnancy the serum estrogens and urinary pregnandiol (part of the substrate) increase progressively, as does the serum concentration of beta-glucuronidase. Just preceding, or immediately following, the onset of pre-eclampsia there is a sudden rise in serum enzyme concentration, but this gradually declines during a period when hormone levels are reported as decreased.⁹⁻¹¹ In this study only one patient without pre-eclampsia had consistently high levels of enzyme, 56 to 59 μg per cubic centimeter. In this case the last menstrual period occurred in January, 1946, and delivery in May, 1947, an amenorrhea of seventeen months' duration.

The high levels of beta-glucuronidase during pre-eclampsia is probably not due to failure of excretion. One patient with a terminal uremia had a level of 5.6 μg per cubic centimeter, within the range for the nonpregnant individual.³⁵

From the results of this study it would seem serum beta-glucuronidase levels could be used to differentiate pre-eclampsia from hypertensive toxemia. But of possible greater importance would be its use to delineate those patients with excessive weight gain who are destined to develop pre-eclampsia from those who are not. Ordinarily prenatal patients visit this clinic every three weeks for the first thirty-four weeks and every two weeks thereafter. The increased frequency of visits during the last trimester is partly because a pre-eclampsia might occur. Serum beta-glucuronidase determinations, obtained at three-week intervals, after twenty-eight weeks' gestation, might warn the obstetrician previous to such an eventuality.

Although the method of preparation of the substrate is difficult, the colorimetric analysis of the enzyme is easy enough for the average laboratory technician. Difficulties with the substrate could be solved by commercial preparations of that substance. It remains stable, as does the serum enzyme. The method of analyses is accurate, being reported within 2 per cent.³⁶

Conclusions

1. Serum beta-glucuronidase levels will differentiate most cases of presumable pre-eclampsia and hypertensive toxemia of pregnancy.
2. Glucuronidase levels may warn the obstetrician of an impending pre-eclampsia.
3. The serum concentration of the enzyme does not reflect the severity of the toxemia.

4. Levels during convulsive toxemia are not diagnostic.

5. The serum concentration of beta-glucuronidase apparently reaches a maximum just before, or early in the course of, pre-eclampsia, and then falls during the duration of the syndrome.

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Discussion

DR. CARL P. HUBER, Indianapolis, Ind.—Anything which serves to differentiate the toxemias of pregnancy into their various groups is certainly worthy of complete investigation. The results reported in this paper seem to give a clue along that line. The authors show very definitely that serum beta-glucuronidase levels are, on the average, above the normal line in the pre-eclamptic group of patients and that in the hypertensive patients they average much lower. It would appear that studies along these lines would be of definite value in differentiating these two groups of pregnant patients and would serve to reinforce our clinical interpretation concerning them. More important perhaps is the observation which is made in the latter part of the paper in which it is shown that among those patients with

excessive weight gain it is possible to pick out the group destined to develop additional evidence of pre-eclampsia by the study of beta-glucuronidase levels. It is quite obvious that we will have to learn a great deal more about the enzymes if we are going to understand many of the complications that arise in pregnancy and that have previously been obscure.

Glucuronidase is one of the enzymes essential in various phases of carbohydrate metabolism and is very probably an important factor in progestin and estrogen metabolism. Its study, therefore, is a step in the investigations that have been made concerning hormone levels during pregnancy and in the toxemias of pregnancy. It is only one step, however, and it does not completely explain the variations that have occurred. Like all catalysts, glucuronidase may act in one of two directions. The mere fact that in the pre-eclamptic toxemia of pregnancy there is a high level of glucuronidase in the serum does not mean that there has been an increased metabolism of the estrogens and progestin. It may mean that there has been a failure of the utilization of the glucuronidase due to some lack of intermittent steps that may be associated with their metabolism. It does not even necessarily mean that there is any connection with hormone metabolism, but these changes may be associated with the metabolism of other toxic products that are produced in pre-eclamptic patients. A great deal more work obviously must be done before we have a complete understanding of the situation.

Dr. Odell did not give any description of the complicated procedures associated with the test, and from the practical standpoint for those who do not have the same laboratory facilities that are available at Chicago Lying-in Hospital the performance of the test would as yet be of considerable difficulty. The actual determination of glucuronidase, as I understand it, depends upon a calorimetric method which is not difficult. Obtaining the substrate upon which that reaction is based is, however, very complicated. I am informed that the method is to feed rabbits phenolphthalein and collect the urine over a period of days, and from that urine there is then extracted a phenolphthalein glucuronidate which is purified by a number of processes so that other excretory products are eliminated. It is only then that one has available a substrate on which the test can be performed. I point out that these operations are now extensive and that phenolphthalein glucuronidate will undoubtedly soon be commercially available either as a biologic product or as a synthetic product. When that time comes a great many more of us can undertake such studies, and increased information concerning their value will rapidly become available.

DR. ODELL (Closing).—The test for beta-glucuronidase was originally designed for use in cancer. Patients with cancer have some increase in tissue level, although not consistently so. To date there have been no conditions giving as high serum values as pregnancy, or toxemia of pregnancy.

The reason for the increase in serum enzyme concentration during pregnancy and toxemia of pregnancy should become of considerable interest. We analyzed the vital organs of two women expiring near term. The enzyme concentration of these tissues gave no clue as to origin. Since the highest concentration in the blood lies in the buffy coat, future investigation may lie in that direction.

FACE PRESENTATION*

A Study of 160 Cases

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LITTLE has been written, especially in America, concerning the problems of face presentation, although the dangers of, and consequences from, mento-posterior deliveries are generally recognized and feared. The scant literature is evidence of the lack of experience that the clinical observer has had with this condition. Obstetric centers have been somewhat remiss in reporting their accumulated results in its management, and the greater part of present-day thought and teaching has been dictated by the eminent obstetricians of the nineteenth century. Reports of several small series have appeared in recent years, and the authors have set up the results obtained in these few cases as examples for the management of the condition in general.

A brief résumé of the literature reveals that, in 1941, Mussio and Walker¹ suggested that conversion of mentoposteriors to vertex occiput anteriors was the safest form of delivery for the mother and child, and gave as their reason for this opinion the maternal mortality of 11.6 per cent obtained by Reed in 1905, with an infant loss of 40.6 per cent in this position. On the other hand, DeLee² concluded that "mentosacral positions terminating happily for the mother and child are so exceedingly rare that, for practical purposes, it is best to consider them absolutely impossible and as always requiring interference from art." That untoward complications are not infrequent in face presentations is given further evidence by the report of Gill,³ in 1944, of dystocia caused by a fore-lying elbow. The most comprehensive recent study of face presentations is the series compiled by Posner and Buch,⁴ in 1943, in which 87 cases were reported from the Harlem Hospital. They concluded that, because of the "high maternal and fetal morbidity and mortality and the greater incidence of disproportion and prolonged labor with dystocia accompanying extension of the head, cesarean section should be given greater consideration than heretofore in early diagnosed cases of face presentation, especially in primiparae."

This report will be concerned with the results obtained in 160 cases which occurred on the combined services of the Charity Hospital of Louisiana, in New Orleans, during the twenty-five years ending with December, 1946. The total number of deliveries during this period was 88,114, making an incidence of face presentations of 0.184 per cent, which compares with 0.19 per cent reported by Posner and Buch,⁴ and 0.25 to 1 per cent generally given as the incidence in most texts. This incidence is comparable to that found by Kemp,⁵ in 1859, when he reported two cases in an analysis of 1,000 deliveries occurring in Baltimore.

*Read before the Central Association of Obstetricians and Gynecologists, Louisville, Kentucky, Oct. 23-25, 1947.

The purpose of this study is to analyze the comparative results obtained by the several methods that have been used in the management of this presentation, in the hope of deducing from it a sounder policy for handling this relatively uncommon, but often difficult, obstetric problem (Table I).

TABLE I. FREQUENCY

| | AUTHOR'S SERIES | HARLEM HOSPITAL SERIES | COMBINED SERIES |
|-------------------|--------------------|---------------------------|--------------------|
| Total deliveries | 88,114 | 48,000 | 136,114 |
| Face presentation | 160 | 87 | 247 |
| Incidence | 0.184 | 0.19 | 0.187 |

Table II gives age and parity for the series and shows that the condition is about three times as frequent in multiparas as in primiparas, the ratio being 119 to 41, respectively. It is also seen that in patients 20 years of age or younger, it occurs much more commonly in primiparas (24 cases) than in multiparas (13 cases) a ratio of 2 to 1; between the ages of 21 and 30 years, in 82 cases, there were 13 primiparas and 69 multiparas, a ratio of 1 to 5; and over 30 years of age, the relative frequency was 4 primiparas to 37 multiparas, a ratio of 1 to 9.

TABLE II. AGE AND PARITY

| | PRIMIPARAS | MULTIPARAS | TOTAL |
|-------------------|------------|------------|-------|
| 20 years or less | 24 | 13 | 37 |
| 21-30 years | 13 | 69 | 82 |
| 31 years and over | 4 | 37 | 41 |
| Total | 41 | 119 | 160 |

The frequency of the various positions is shown in Table III. Engagement was in the right oblique diameter in 82 cases (65 left mentoanterior and 17 right mentoposteriors), while in 45 cases it was in the left oblique diameter (18 left mentoposteriors and 27 right mentoanterior). Transverse position and those in which the position was not diagnosed accounted for 33 cases. The ratio of primiparas to multiparas for the various positions paralleled the incidence of each in the series except in mentoposteriors, which accounted for 35 cases, of which 15 were primiparas and 20 multiparas.

TABLE III. POSITIONS

| | PRIMIPARAS | MULTIPARAS | TOTAL |
|-----------------------|------------|------------|-------|
| Left mentoanterior | 12 | 53 | 65 |
| Left mentotransverse | 3 | 5 | 8 |
| Left mentoposterior | 8 | 10 | 18 |
| Right mentoanterior | 3 | 24 | 27 |
| Right mentotransverse | 0 | 6 | 6 |
| Right mentoposterior | 7 | 10 | 17 |
| Position not stated | 8 | 11 | 19 |
| Total | 41 | 119 | 160 |

Etiology

In reviewing the records, wherever possible, either by inference or by an actual note, an effort was made to arrive at some conclusion as to the cause of the presentation. The results of this tabulation are found in Table IV. Contrary to the findings of others, contracted pelvis was the chief etiological factor in only 6 cases and a large baby accounted for 8 more, making a total of 14 cases in which disproportion could be considered the principal factor in the causation

of the presentation. It is noteworthy that 52 of the cases occurred in women where parity (fourth or more pregnancy) was a major factor, and that 9 cases were anencephalic monsters; and 12 followed primary brow presentations. There were 56 cases, 22 being primiparas, in which no reason was evident for the presentation. This is at variance with Beek,⁶ who states that in his experience he has seen only one primary face presentation.

TABLE IV. ETIOLOGY

| | PRIMIPARAS | MULTIPARAS | TOTAL |
|----------------------------------|------------|------------|-------|
| Parity only (4th baby or more) | 0 | 43 | 43 |
| Parity with another factor | 0 | 9 | 9 |
| Hydramnios | 0 | 1 | 1 |
| Compound presentation | 1 | 2 | 3 |
| Second twin | 1 | 0 | 1 |
| Secondary to brow | 4 | 8 | 12 |
| Cord about neck | 0 | 2 (brow) | 2 |
| Small babies* | 4 | 14 | 18 |
| Large babies | 2 | 6 | 8 |
| Uterine tumor | 0 | 1 | 1 |
| Marginal placenta previa | 0 | 1 | 1 |
| Not explained | 22 | 34 | 56 |
| Pendulous abdomen | 0 | 4 | 4 |
| Small pelvis | 4 | 2 | 6 |
| Incompressible pyelitis† | 1 | 0 | 1 |
| Monster | 3 | 6 | 9 |
| Following bag induction of labor | 0 | 1 | 1 |

*Two 6 month fetuses weighing less than 5½ pounds.

†Porro section.

Dilatation of the Cervix

Dilatation of the cervix was obtained, as is shown in the following table (Table V) in 152 cases, where delivery was per vaginam:

TABLE V. DILATATION OF CERVIX

| | PRIMIPARAS | MULTIPARAS | TOTAL |
|---------------------------------------|---|---|-------|
| Average spontaneous (0-24 hours) | 27 | 94 | 121 |
| Long spontaneous (24 hours or longer) | 6 { 2 RMA 2 LMA 1 LMP 1 Not stated | 14 { 7 LMA 2 RMT—10 days 3 RMP 1 RMA 1 Not stated—impacted face with foot | 20 |
| Duration not stated | 1 (RMP) | 2 (LMA) | 3 |
| Dührssen's | 1 (LMA—bag failed) | 0 | 1 |
| Bag | 1 (LMP) | 3 (2 LMA) (1 LMP) | 4 |
| Manual dilatation | 1 (LMA) | 1 (LMT) | 2 |
| Breech (Braxton Hicks' version) | 0 | 1 (LMA) | 1 |

Of the 27 cases where dilatation was delayed or obtained by operative means, 14 in 92 (15 per cent) were mentoanterior, 7 in 35 (20 per cent) were mentoposteriors, and 3 in 14 (21 per cent) were mentotransverse, and in 3 cases, the position was not stated. It appears, therefore, that the fetal position had little effect on the ease with which dilatation was obtained.

Methods of Delivery

Several separate methods or combinations were employed in the delivery of the babies:

1. *Spontaneous as Face Presentation*.—(Infant mortality, 14.3 per cent, maternal mortality, 0.) Eighty-six cases delivered spontaneously as a face, either relatively easily or following a difficult labor. Thirteen were primiparas who ended with 3 monsters, 1 macerated fetus, and 2 in which the death was not explained, an incidence of infant death of 2 in 9 viable babies. Among the 73 multiparas, there were 1 macerated fetus and 3 monsters. Of these 69 babies alive before birth, 5 died either because of, or during, labor (one being a 6-month fetus), and 5 others died before the mother was discharged from the hospital. The total gross infant mortality for the entire spontaneous group was 12 (15.6 per cent), and the corrected 10, or a corrected infant mortality rate of 14.3 per cent. This is shown in the following table:

TABLE VI, A. SPONTANEOUS DELIVERY—86 CASES

| | PRIMIPARAS | MULTIPARAS |
|--|----------------|---------------------|
| <i>Total number of cases</i> | 13 | 73 |
| Monsters | 3 | 3 |
| Macerated babies | 1 | 1 |
| Babies died at birth | 0 | 5 |
| | | (1 six-month fetus) |
| Neonatal deaths | 2 | 5 |
| Gross infant mortality | 5 in 12 39% | 14 in 73 19.1% |
| Corrected infant mortality | 2 in 9 22% | 9 in 68 13.2% |
| <i>Positions (exclusive of 6-month fetus)</i> | | |
| Left mentoanterior | 2 | 36 |
| Left mentotransverse | 1 | 2 |
| Left mentoposterior | 4 | 8 |
| Right mentoanterior | 2 | 21 |
| Right mentotransverse | 0 | 1 |
| Right mentoposterior | 1 | 0 |
| Position not stated | 3 | 5 |
| Average corrected infant mortality was 14.3 per cent | | |

2. *Low Forceps to the Face*.—(Infant mortality, 12.5 per cent, maternal mortality, 0.) This operation was employed 16 times (8 primiparas and 8 multiparas). The results of this form of delivery are shown in the following table:

TABLE VI, B. LOW FORCEPS TO FACE—16 CASES

| | PRIMIPARAS | MULTIPARAS |
|--|------------|------------|
| <i>Total number of cases</i> | 8 | 8 |
| Babies dying at birth | 2 | 0 |
| Neonatal deaths | 0 | 0 |
| Gross infant mortality | 25% | 0 |
| Corrected infant mortality | 25% | 0 |
| <i>Positions:</i> | | |
| Left mentoanterior | 4 | 5 |
| Left mentotransverse | 1 | 0 |
| Left mentoposterior | 1 | 0 |
| Right mentoanterior | 1 | 1 |
| Right mentotransverse | 0 | 0 |
| Right mentoposterior | 0 | 2 |
| Position not stated | 1 | 0 |
| Corrected infant mortality for low forceps group was 12.5 per cent | | |

3. *Flexion of Head*.—(Infant mortality followed by high forceps, 40 per cent, by other methods, 0; maternal mortality, 0.) Flexion of the head was done in 15 cases, followed by spontaneous delivery in 5. Table VI, C shows the results where flexion was used, followed by spontaneous and forceps delivery.

The average corrected mortality in this group of cases was 14.3 per cent. Flexion was tried unsuccessfully in 16 additional cases which were delivered by some other method.

TABLE VI, C. FLEXION OF HEAD—15 CASES

| FLEXION DELIVERIES | TOTAL NO. OF CASES | | POSITIONS | INFANT MORTALITY | CORRECTED MORTALITY |
|--------------------------|--------------------|------------|---|---------------------|------------------------|
| | PRIMIPARAS | MULTIPARAS | | | |
| Spontaneous | 1 | 4 | 1 right mentopost. 1 left mentotrans. 1 left mentoant. 1 right mentotrans. 1 not stated | 0 | 0 |
| Low forceps | 2 | 1 | 1 right mentopost. 1 left mentopost. (macerated) 1 left mentoant. | 1 | 0 |
| Midforceps (Scanzoni) | 0 | 2 | 2 right mentoant. | 0 | 0 |
| High forceps | 0 | 5 | 4 right mentopost. 1 not stated | 2 | 40% |

4. *Midforceps to the Face*.—(Infant mortality, 0, maternal mortality, 0.) This was used on one primipara (left mentoanterior) where flexion had failed, and resulted in a live baby.

5. *Version and Extraction*.—(Infant mortality, 53.3 per cent; maternal mortality, 3.5 per cent.) Version and breech extraction were employed in 27 cases. The results are shown in Table VI, D.

TABLE VI, D. PODALIC VERSION AND BREECH EXTRACTION—27 CASES

| | PRIMIPARAS | MULTIPARAS |
|---|--|--|
| Elective | 7—1 easy, 6 difficult 2 RMP 1 LMA 1 LMP 3 Not stated | 10—4 easy, 6 difficult 4 LMA 1 LMP 2 RMT 2 RMP 1 Not stated |
| After failure of flexion or/and forceps | 4 { 3 LMA 1 RMP | 6 { 2 LMA 2 LMT 1 LMP 1 RMP |
| Total | 11 | 16 |
| Gross infant mortality | 9 (1 macerated) | 6 |
| Corrected infant mortality | 8 in 10 80 per cent | 6 in 16 37.5 per cent |
| Average corrected mortality for primiparas and multiparas—53.3 per cent | | |

In one multipara and two primiparas there was evidence of fetal distress before beginning the operation. In the former, flexion and forceps were tried unsuccessfully and the heart tones were 170+ per minute. In the first primipara,

a bag had been used to obtain dilatation, high forceps had failed, and the heart tones were also 170+ per minute; in the second primipara the fetal heart was irregular and flexion had also failed. In a third primipara, the baby had been dead for some time before the operation was begun. The remainder of the babies were in good condition at the time the versions were undertaken.

The length of labor in these cases varied, as is shown in Table VI, E.

TABLE VI, E. DURATION OF LABOR IN 27 VERSION DELIVERIES

| | | BABIES LIVED | | BABIES DIED | TOTAL |
|--------------------|------------|--------------------------------------|--|-------------|-------|
| Less than 10 hours | Primiparas | 1 (2nd twin) | 1 (difficult labor) | | 2 |
| | Multiparas | 1 | 3 (1 membranes ruptured 3½ hours) | | 4 |
| 11-20 hours | Primiparas | 1 (right mento-posterior) | 5 (3 2nd stage, 7 lb. 6 oz., 5 hours) (1 poor condition, 2nd stage 2½ hours) (1 macerated) | 6 | |
| | Multiparas | 5 | 1 | | 6 |
| Over 21 hours | Primiparas | 0 | 2 (1 difficult 28½ hour labor) (1 difficult 48 hour labor) | 2 | |
| | Multiparas | 3 (1 mentosacral and prolapsed foot) | 1 (2nd 5 hours, membranes ruptured short time) | | 4 |
| Time not stated | Primiparas | 0 | 1 | | 1 |
| | Multiparas | 1 | 1 | | 2 |

In four primiparas, the membranes had been ruptured for 5, 8, 10, and 48 hours before the version was attempted, ending with 3 stillborn babies and one baby in poor condition, who later died. In another primipara, the membranes had been ruptured 12 hours without complete dilatation; following accoucheement forcé, a version and extraetion were done, resulting in a dead baby, the mother also dying of sepsis after twenty-five days. In one multipara, after the membranes had been ruptured for nine and one-half hours, a difficult version netted an infant with intraeranian hemorrhage, who lived, following several spinal punctures. In two primiparas, the membranes were ruptured two hours or less, and resulted in living babies, while two babies were lost in the three multiparas in whom the membranes had been ruptured for this duration of time. There were one primipara and one multipara in whom the membranes were ruptured for two to three hours before the version was attempted and both babies died. In the cases of three primiparas, the duration of the time of rupture of membranes before the version and extraetion was not stated. They yielded a macerated fetus and two stillbirths, while two babies were dead at delivery in the 7 multiparas belonging to this group.

6. *Cesarean section*.—(Infant mortality, 0, maternal mortality, 0.) This method of delivery was used in 8 cases, 4 primiparas and 4 multiparas. All the mothers and babies survived. In one primipara, a cesarean hysterectomy was done because of an incompressible pyelitis in an ectopic kidney. The postoperative course in this case was stormy. Of the three other primiparas, two had elective sections and the other, with a small pelvis, was sectioned after an unsuccessful trial of labor. One multipara with a small pelvis was sectioned after a trial; two were repeat sections; and in another, which began as a brow presentation, a section was done when labor failed to progress after thirteen hours.

7. *Manual Rotation*.—Manual rotation followed by low forceps was used in one multipara, a right mentoposterior, in whom the membranes were ruptured at the time of the procedure. The condition of the baby and mother was good.

8. *Monsters*.—(Infant mortality 100 per cent, maternal mortality, 0.) Of the 3 primiparas and 6 multiparas who had anencephalic monsters, delivery was difficult in 3 of the multiparas. Low forceps were used in one, Braun's hook about the neck of the second, and a cephalic manual extraction was done on the third. The remainder were spontaneously delivered.

9. *Craniotomy*.—(Infant mortality, 100 per cent, maternal mortality, 33½ per cent.) Three multiparas were delivered by this destructive method. In one, a right mentotransverse, the patient had been in labor for ten days when she was admitted with a temperature of above 100.4 F. On admission, the heart tones were normal. Thirty hours after the membranes ruptured, however, the craniotomy was done. The second case was a grand multipara (para viii, gravida ix) with a right mentoposterior, who, after 32 hours of labor, went into shock following a sacral block. The death of the baby in this case was considered as being due to anoxia. The third case was admitted with a temperature range of 101° to 103° F., the membranes ruptured. After forty-eight hours of labor, the heart tones disappeared. The cervix was only partially dilated and the head was impacted, necessitating the craniotomy. This patient died of peritonitis on the sixth postpartum day.

Anesthesia

It was not possible to give an anesthetic in 24 cases, in which delivery occurred sooner than expected. The majority of the remaining cases were anesthetized with chloroform or ether, the latter, either alone or in combination with ethylene or nitrous oxide. Generally, the more difficult the operative procedure, the more profound the anesthetic.

Maternal Morbidity*

The following table (Table VII) gives the maternal postpartal course.

Two points are outstanding in the morbidity study: First, the more complicated the delivery, the more morbid the patient. Almost 50 per cent of those having versions and extractions and high forceps following flexion were morbid,

TABLE VII. MATERNAL MORBIDITY

| | MORBID | | NOT MORBID | | NOT STATED | |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | PRIMIP- ARAS | MULTIP- ARAS | PRIMIP- ARAS | MULTIP- ARAS | PRIMIP- ARAS | MULTIP- ARAS |
| <i>Methods of delivery:</i> | | | | | | |
| Version and extraction | 7 | 5 | 3 | 11 | 1 | 0 |
| Low forceps | 1 | 6 | 9 | 4 | 0 | 0 |
| High or midforceps | 2* | 1 | 0 | 2 | 0 | 1 |
| Spontaneous delivery and other | 3† | 11 | 10 | 70 | 0 | 0 |
| Cesarean section | 2‡ | 0 | 1 | 4 | 0 | 1 |
| Craniotomy | 0 | 3 | 0 | 0 | 0 | 0 |
| Total number of cases | 15 | 26 | 23 | 91 | 1 | 2 |
| Long labor | 5 | 8 | 3 | 11 | 0 | 0 |

*One Dührssen's and 1 flexion.

†One third degree tear.

‡One Porro section.

*In determining morbidity, the standard set up by the American Committee on Maternal Welfare was used.

while less than 20 per cent of the spontaneous deliveries for both primiparas and multiparas ran a temperature elevation. Second, one-third of the morbid primiparas and multiparas had labors that lasted twenty-four hours or longer, while in the nonmorbid group, approximately one-eighth of each had labors of this duration. Two cesarean sections in primiparas were followed by a temperature elevation; one was the patient with the ectopic kidney, who had the Porro section. Two of the three patients having craniotomies were morbid for 3 to 14 days each and recovered, while the third one died of sepsis six days after the delivery. The remainder of the morbid cases ran a slight to marked temperature elevation for 1 or 2 days to as long as 25 days.*

There were 11 postpartum patients (3 primiparas and 8 multiparas) who bled excessively or were in shock. Of these, 5 (2 primiparas and 3 multiparas) were delivered by version and breech extraction; 2 had high forceps (1 primipara and 1 multipara, the primipara following Dührssen's incisions); 3 multiparas were delivered by craniotomies; and one multipara delivered spontaneously.

TABLE VIII. POSTPARTUM, HEMORRHAGE AND SHOCK—11 CASES

| | PRIMIPARAS | MULTIPARAS |
|------------------------|-------------------------------|------------|
| Version and extraction | 2 (1 manually dilated cervix) | 3 |
| High forceps | 1 (Dührssen's) | 1 |
| Craniotomy | 0 | 3 |
| Spontaneous delivery | 0 | 1 |
| Total | 3 | 8 |

TABLE IX. CERVICAL AND PERINEAL LACERATION

| | PRIMIPARAS | MULTIPARAS |
|----------|--|--|
| Cervix | 1 (Version and extraction, manually dilated cervix) | 7 { 3 spontaneous deliveries 2 version and extraction 1 high forceps, long labor 1 craniotomy |
| Perineum | 7 { 1 first degree: version and extraction 3 second degree 1 spontaneous delivery 2 version and extraction 3 third degree 2 version and extraction 1 high forceps, Dührssen's incision | 17 { 11 first degree 1 high forceps 10 spontaneous delivery 5 second degree 1 craniotomy 2 version and extraction 1 high forceps 1 third degree: spontaneous delivery |

Maternal Mortality

Two mothers were lost in the 160 cases. The first, in 1929, was a Negro gravida 4, with a mentoposterior, who was admitted in labor several days after the membranes had been ruptured. The temperature on admission was 100° to 101° F. At the end of forty-eight hours, the cervix was almost completely dilated and the face was impacted in the mentosacral position. The uterus was tightly molded about the baby. A craniotomy was chosen for the delivery. The patient died six days later of puerperal sepsis and general peritonitis. The second maternal death was one of the cases in 1934, a 20-year-old Negro primipara with an adequate pelvis, who was admitted in labor. After seventeen hours of

*One patient, who had a version and extraction following manual dilatation, died on the twenty-fifth day.

labor, the membranes ruptured, and an arm prolapsed, complicating the left mentoanterior position. This was followed by evidence of fetal distress. The cervix was undilated; a manual dilatation was attempted followed by a version and extraction, using nitrous oxide only for the anesthetic. The baby could not be revived. The mother became septic, developed a right femoral thrombophlebitis, and died on her twenty-fifth postpartum day.

The first case probably was handled as conservatively as the 1929 armamentarium would have permitted, unless a Porro section had been used, but the second case is a striking example of poor obstetric management and violates the conditions needed for successfully doing versions and extractions. With penicillin, sulfonamides, and streptomycin, as well as improved technique, a section on either of these cases would have been safer, employing a hysterectomy on the first and the extraperitoneal technique on the second.

Condition of Babies

The conditions of the babies at birth are shown in Table X, while Table XI summarizes the infant loss, and Table XII outlines fetal abnormalities in living babies found at birth.

One multipara finally delivered a live baby with low forceps, after twenty-four hours, the face being traumatized. The baby of another multipara was alive but had a marked cleft palate and harelip. A third multipara, after twenty-two hours of labor, delivered a normal baby with edema of the glottis. The position in this case was a left mentoposterior. In still another multipara, following a version and extraction, the baby had a fractured clavicle; while the baby of

TABLE X. CONDITION OF INFANTS IN TYPES OF DELIVERY

| | LIVING | | STILLBIRTH | | NEONATAL | | MACERATED | | MONSTER | |
|------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | PRIMIPARAS | MULTIPARAS | PRIMIPARAS | MULTIPARAS | PRIMIPARAS | MULTIPARAS | PRIMIPARAS | MULTIPARAS | PRIMIPARAS | MULTIPARAS |
| Mid and high forceps | 1 | 5 | 0 | 2 | 1 | 0 | 1 | 0 | 0 | 0 |
| Version and extraction | 4 | 11 | 6 | 5 | 1 | 1 | 1 | 0 | 0 | 0 |
| Spontaneous delivery | 10 | 69 | 0 | 5 | 1 | 24 | 0 | 3 | 3 | 65 |
| Low forceps | 10* | 8 | 0 | 1 | 24 | 0 | 1§ | 0 | 0 | 0 |
| Cesarean section | 4 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Long labor | 5 | 15 | 2 | 4 | 0 | 0 | 1 | 0 | 0 | 0 |

*One followed version.

†One premature.

‡One 2½ pound baby; 1 6-month pregnancy.

§Head flexed.

||One hydramnios; 1 4 pounds.

¶Three difficult deliveries.

TABLE XI. INFANT MORTALITY

| | PRIMIPARAS | MULTIPARAS |
|---|-----------------------|-----------------------|
| Total number of babies | 41 | 119 |
| Less monsters, macerated, and prematures | 5 | 11 |
| Net viable | 36 | 108 |
| Fetal loss at delivery and during neonatal period | 10 (27.7 per cent) | 15 (13.9 per cent) |
| Percentage loss: viable babies, 17.3 per cent | | |

TABLE XII. ABNORMALITIES IN LIVE BABIES AT BIRTH

| | |
|---------------------------|---|
| Trauma to face | 1 (para iv, 24½ hour labor, LMA, low forceps, baby lived) |
| Fractured clavicle | 1 (para iii, 3½ hour labor, version and extraction under ether, baby lived) |
| Hair lip, cleft palate | 1 para ii, LMA, spontaneous delivery 7½ hour labor, baby lived) |
| Severe moulding head | 1 (para ii, RMA, spontaneous delivery 37½ hour labor, baby lived) |
| Face markedly cyanotic | 3 (para ix, RMA, spontaneous delivery 40 hour labor, baby lived; para i, LMA 21+ hour labor; para iv, RMP spontaneous delivery) |
| Edema of glottis | 1 para vi, LMP, spontaneous delivery 9 hour labor, baby lived) |
| Intracranial hemorrhage* | 1 (para i, grvida iv, elective version in RMP) |
| Condition poor (asphyxia) | 1 (para 0, LMA, version and extraction following bag) |

*Several other babies in the later neonatal period exhibited signs of intracranial hemorrhage while their immediate postpartum condition was poor.

a fifth multipara, delivered by version and extraction, had an intracranial hemorrhage, but survived after receiving several cysternal and spinal taps. Although none of the abnormalities listed were permanent (except the lip-palate imperfection) any one of them could have been associated with a fetal intracranial hemorrhage, or a lifelong disabling deformity might have resulted.

Discussion

A. *Incidence*.—It appears that the incidence of face presentations stated in our obstetric texts is too high and probably should be revised. Although that found in this series compares with that of others, it is possible that a number of cases beginning as face were converted into vertex, the original presentation being forgotten.

In this series there were 92 (57.5 per cent) mentoanterior, 35 (22 per cent) mentoposterior, 13 (9 per cent) mentotransverse, and 13 (12 per cent) in which the position was not stated, which compares with 50.3 per cent, 23 per cent, 13 per cent, and 14 per cent respectively reported by Posner and Buch.

B. *Etiology*.—Disproportion, although present in 14 cases, did not play a major role in the production of the presentation, which is at variance with general opinion and the incidence of 2 out of 3 cases, as given in the Harlem report. Multiparity does seem to play a major role and occurred alone or in combination with other factors in 52 cases. Of this number, 14 patients were grand multiparas, having their seventh to fifteenth baby. Brow presentations preceded complete extension of the head in 12 cases. Other factors, such as pendulous abdomen, fetal neck tumors, hydramnios, placenta previa, small babies, compound presentation, and the use of the hydrostatic bag in the first stage of labor, probably do predispose to face presentation and their presence should

keep one alert for this condition, although in this series their occurrence was infrequent.

C. Management.—Early diagnosis is important. In the majority of these cases, the diagnosis was made after labor was well advanced, yet several were diagnosed before the onset of labor. Primary face presentations should be recognizable by careful abdominal palpation and vaginal examination, confirming if necessary by x-ray. The important findings are concave dorsal plane, prominent small parts, loud fetal heart tones heard best through the anterior fetal chest wall, and the presence of a marked cephalic prominence on the same side of the baby as is the back; vaginally, the facial features are not to be confused with the breech. This, combined with multiparity, especially grand multiparity, disproportion, and other more or less uncommon conditions, should lead to an earlier diagnosis and, therefore, a less complicated labor and delivery.

Labor should be conducted guardedly and aseptically, for many face presentations are potential candidates for cesarean section. Fluids, sedation, and care of the bladder and rectum are more important than in vertex presentations. The first stage of labor is likely to be prolonged; the longest in this series was 10 days, ending with a craniotomy.

Since spontaneous delivery does occur in all positions, it should probably be anticipated if there is no disproportion, but interference (low forceps to face or following flexion, midforceps to face, flexion alone, and manual rotation) should always be kept in mind as a possibility for a safe termination of labor. Early flexion of the head in mentoposteriors, under anesthesia and aseptic technique, is probably preferred in multiparas and an occasional primipara, allowing labor to progress normally afterward. The Schatz, Ziegenspeck, and Thorn maneuvers may be useful. Failing to accomplish flexion, cesarean section is infinitely better than to attempt delivery by the breech.

This last method is the least desirable of all methods for delivery. Although it was used in this series in 10 cases where other methods failed, the fetal results were almost as poor when done electively. The attitude of the fetus, duration of labor, and the possibility of long-standing ruptured membranes presage an unhappy ending for the baby and danger to the mother, and predispose to violation of the conditions under which this operation may be expected to be successfully done. Delivery of one second twin in this series by elective version and extraction was apparently justified. Perineal and cervical tears, hemorrhage, sepsis, damage to the living fetus were most common in the cases where this operation was done. One of the maternal deaths was due directly to this method of delivery, where poor judgment was noted and obstetric hysteria was evident. Certainly, waiting or cesarean section could have produced no worse results.

The suggestion made by Posner and Buch⁴ that cesarean section should be done more often, especially in primiparas, is borne out by the results herein reported, and should be made to include (1) face presentations in multiparas having more than the fifth or sixth baby, (2) any case where the first stage is not progressing satisfactorily, (3) when conditions found during the second

stage are not favorable, rather than taking a chance with the two lives involved. The availability of sulfonamides, antibiotics, and the extraperitoneal cesarean technique makes conservatism justifiable in the remainder of the cases. This should eliminate the necessity of craniotomies and other mutilating operations. However, death of the fetus in utero and fetal deformities are direct contraindications to this policy and must be eliminated before subjecting the patient to the danger of a cesarean section.

It should be borne in mind that the long labors and difficult operative procedures necessitated by face presentations for vaginal delivery are the chief causes of maternal hemorrhage and infection and fetal death. In at least one case, the baby died during the long labor and was ultimately delivered vaginally.

The anesthetic did not seem to play an important part in the delivery, except when a formidable procedure was undertaken. Version and extraction, high and midforceps, and craniotomies required deeper anesthesia than spontaneous and low forceps deliveries. That this was the case is in line with what would be expected.

Summary and Conclusions

1. The results obtained in the delivery of 160 cases of face presentation are reported.

2. The frequency of face presentation in this series was 0.184 per cent, which is comparable to 0.19 reported in a recent series. Multiparas were three and a half times more common than primiparas and mentoanterior positions were more often seen than other positions.

3. Parity and its accompanying lack of abdominal and uterine tone were the most important etiological factors. However, other conditions must be borne in mind as possible causes, and the presentation should be watched for in contracted pelvises and in patients with large babies. It appears that primary face presentations are not uncommon, there being 56 cases in 160, in which no explanation could be found for the presentation.

4. Spontaneous delivery occurred from all positions and may be anticipated provided there is no disproportion in most multiparas and possibly a few primiparas. In the latter group, cesarean section should be done electively when the diagnosis is clear, after fetal death and deformities incompatible with life have been eliminated. Low forceps to the face or following flexion of the head and manual rotation may be needed to finish the delivery late in the second stage. Versions and extractions should have no place in the delivery of face presentations except in an occasional case of a second twin which presents as a face.

5. The adjusted infant mortality for this series was 17.3 per cent, which could be materially reduced by more carefully watched first and second stages, omission of complicated vaginal procedures when simple procedures failed, and substitution of cesarean section in these cases.

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Discussion

DR. HENRY BAUXBAUM, Chicago.—The greatest value one can receive from a presentation of this kind is a comparative evaluation of the various methods for handling this fairly rare and difficult complication, to employ the method which gives the greatest possibility of success. Dr. Reddoch gives us the results of his arduous studies and makes several pertinent observations. Just to re-emphasize a few of his suggestions: Cesarean section as an elective procedure is becoming more popular in the management of face presentation and rightly so. This operation is particularly indicated in elderly primigravidas, and in cases of cephalopelvic disproportion and persistent mentoposterior presentation. This procedure carries a greater assurance of safety to the mother, as well as a greater fetal salvage, as shown in his tables. Version is extremely difficult as well as quite dangerous to perform in a face presentation, because of the marked extension of the fetal body with the location of the buttocks high in the fundus. The value of x-ray in confirming the diagnosis is unquestionably of great value, as well as to rule out the possibility of a fetal deformity, if a cesarean section is contemplated. I believe that, inasmuch as mentoposterior is an impossible delivery, and may result in an obstetric tragedy if neglected, it is best treated by a cesarean section if the cervix is not dilated, or a conversion, if the condition is recognized after the cervix is completely dilated and effaced. The conversion is done under a deep either anesthesia, after which the patient is allowed to wake up, and labor is permitted to continue until the head molds and dips down deep into the pelvis.

For the purposes of comparison, I would like to refer to the results from the service of the Chicago Maternity Center of face presentation for the past ten years. First, I want to call to your attention the fact that all our cases are conducted in the patient's own home under adverse sanitary conditions. All cases are conducted by an interne who is supervised by a resident, and if necessary an attending physician is summoned. If the delivery is impossible to complete in the home, the patient is hospitalized.

In the period from 1937 to 1946 inclusive, there were 22,440 deliveries, of which 58 cases were diagnosed as face presentation. This is an incidence of 1 to 387 or 0.258 per cent, a slightly smaller incidence than that cited by Dr. Reddoch. Of this group, spontaneous delivery occurred in 42 or 72.4 per cent. Spontaneous delivery following conversion occurred in 2 or 3.4 per cent, making a grand total of 75.8 per cent who delivered spontaneously. One of the latter cases developed an incomplete rupture of the uterus in the right broad ligament, with a subsequent supravaginal hysterectomy followed by recovery. Also, I wish to call attention to the high incidence of prolapse of the cord associated with this type of malpresentation. In the aforementioned 44 cases there were three prolapsed cords and one prolapsed arm. There were three low forceps, two midforceps and two high forceps, for a percentage of 12.1 per cent. Six of these seven cases were preceded by conversion and manual rotation. Version followed by extraction was done four times or in 7.0 per cent of this series. Three of these versions followed a failed conversion. The fetal mortality here was 50 per cent. Craniotomy was performed in two cases or 3.4 per cent. In one of the cases the Center was called in when the patient was fully dilated and had a threatened uterine rupture. She had been previously attended by a midwife and a private doctor. The last case was an anencephalic monster and here extraction of the fetus was accomplished with a Braun's hook, a percentage of 1.7 per cent. In this group there were 7 primiparas and 51 multiparas, a one to seven plus relationship. In spite of or because of the fact that there were no cesarean

sections in this series of face presentations delivered in the home, there was no maternal mortality. Our gross fetal mortality was 27.58 per cent, due to twelve stillbirths and four neonatal deaths. If we count out five anencephalic monsters, two cases in which there were no fetal heart tones audible on arrival of our doctors, and two previable babies under 1,500 grams, our fetal mortality was 12.06 per cent, approximately the same as those of Dr. Reddoch. There were five fetal monstrosities out of 58 cases, a little less than 10 per cent which was the prime etiological factor in the causation of this condition, the so-called snout presentation.

DR. E. L. KING, New Orleans, La.—We have had several cases, both in the hospital and private practice, that have been diagnosed as primary presentation of the face before labor started, but this diagnosis cannot always be made. The x-ray has proved extremely valuable in helping this diagnosis and also in the matter of ruling out an anencephalic monster.

I agree with Dr. Reddoch that more frequent resort to cesarean section in properly selected cases is in order, and I would include in that all cases of face presentation in primigravidas.

DR. RUDOLPH W. HOLMES, Charlottesville, Va.—In the normal, and as well in flat pelves, the characteristic descent in labor is with the chin directed to the side—i.e., the mentobregmatic line is placed transversely; the molding of the head produces a temporary dolichocephalia, and the less the skull bones have ossified, the more marked is such development. Further, the chin will not rotate to the front until the elongated hind head has passed the promontory; therefore, rotation may be so delayed that the mouth may be visible before rotation takes place. This phenomenon of labor in fact is so characteristic, that rotation with forceps never should be assayed until the chin appears under the pubes, from spontaneous rotation. A face presentation, chin at the promontory, may rotate spontaneously if left to nature; a chin in the hollow of the sacrum, likewise, may rotate 180 degrees in the natural course of labor. I have seen several of these instances. Face presentation in eutocia; overly large infants may cause dystocia.

Vaginal vault stenosis due to congenital or acquired lesions makes adequate radium application impossible, and *refusal of radiation* by the patient is occasionally encountered.

Pregnancy complicating cervical neoplasm is a serious matter, and opinions vary as to the best method of treatment. Technically the operation during pregnancy is more difficult as the vascularity of the parts makes oozing more troublesome, though this is to some extent offset by the pliability of the tissues. I have performed Wertheim's operation on three occasions during pregnancy, and one of these patients has survived eight years. The other two patients died within one year of widespread recurrence.

Wertheim's Operation After Previous Irradiation.—On sixty-two occasions I have performed the operation after previous radiation by radium alone, or by a combination of radium and deep x-ray therapy. The intervals between radiation and operation have ranged from one week to fourteen months. This latter was an unusual case which had been fully radiated by local radium and two full courses of deep therapy under the care of Professor Windeyer of the Middlesex Hospital. The patient persistently gave a positive cervical biopsy for adenocarcinoma, and in the end he asked me to attempt a radical abdominal hysterectomy. This was accomplished without any real difficulty together with a thorough clearance of the glandbearing area. The cervix showed undoubtedly active adenocarcinomatous changes, but the glands were negative for growth, and I am quite sure that they had never been involved. In the main, previous radiation does somewhat magnify the technical difficulties of the operation, but, provided the growth still conforms to Stages I or II, in my experience it is always removable. In my opinion it is more than justifiable to attempt such cases, as the alternative to operation is death.

Results of Wertheim Hysterectomy on Cases Selected as Unsuitable for Radiation or Found to be Radioresistant.—During the years 1936 to 1941 in the Chelsea Hospital for Women fifty-four operations were performed in such cases. In all there were 34 Stage I and 20 Stage II growths, and at the end of five years 24 patients, or 44.4 per cent, of the total were known to be alive and well. Six were lost in the follow-up during the first three years of the war. If these be excluded it will be found that 50 per cent of the patients followed up were alive and well. There were three operative deaths in the series—a mortality rate of 5.5 per cent. It must be remembered that these cases were selected as being either unsuitable for radiation or as being proved radioresistant cases. The number who would have survived without operation is impossible to assess.

The Regional Glands.—So far as we can assess, we have come to the conclusion that the rate of carcinomatous gland involvement is approximately as follows:

| | |
|-----------|------------------|
| Stage I | 20-25 per cent |
| Stage II | 30-35 per cent |
| Stage III | 40-50 per cent |
| Stage IV | Over 60 per cent |

These figures are based on material obtained from the Wertheim operation, from the operation of lymphadenectomy without removal of the uterus and from autopsy material, and these figures appear to agree with some other observers.

It would appear obvious that treatment by radium alone using vaginal applicators only can never hope to give adequate radiation to the lymphatic field of the pelvis. Some workers even question the efficiency of deep ray therapy in this respect. At the risk of incurring the enmity of the radiotherapists here I make so bold as to suggest that this ability to sterilize the pelvic lymphatic field of carcinomatous deposits is not so great as many of them think. I feel so strongly about this that I often wonder if the improvement in the results of

other hospitals and nursing homes, have performed Wertheim's operation 207 times with six operative deaths, a mortality rate of under 3 per cent. This is not a tribute to any exceptional operative skill, but to a careful selection of cases, improved anesthesia, the use of blood transfusion and plasma infusions, the use of penicillin and the sulfonamides, and, not least of all, to good nursing.

Thus it will be seen that since 1936 on an average 14 per cent of the patients with carcinoma of the cervix have been subjected to the Wertheim operation, 9 per cent being the lowest in any one of the years, and 20 per cent being the highest rate. Previous to this 55 per cent of all cases presenting were operated upon, whereas Bonney in his own personal series considered that he operated upon 63 per cent of the patients presenting.

From the above it appears that operative treatment is now embarked upon in about one case in seven, whereas originally every alternate patient was subjected to surgery. Our selection of cases for the radical operation is confined to the cases shown in Table VI.

TABLE VI. INDICATIONS FOR WERTHEIM HYSTERECTOMY TODAY

- | |
|--|
| 1. Radioresistant growths proved either clinically or cytologically (biopsy positive). |
| 2. Columnar celled carcinoma of the cervix. |
| 3. Stenosis of vaginal vault. |
| 4. The presence of large fibroids or ovarian cysts complicating cervical cancer. |
| 5. Salpingitis complicating cervical cancer. |
| 6. Refusal of radiation by the patient. |
| 7. Pregnancy complicating cervical cancer. |

Radioresistance.—So far as we know at the moment the most reliable method of determining radioresistance is on clinical grounds, and we have all met with the growth which fails to improve clinically after radiation or which, after appearing to heal, breaks down relatively quickly. Repeated biopsies confirm the diagnosis of resistance. Many attempts have been made on histologic grounds at an early stage of radiation to determine early resistance, and Koller working at the Royal Cancer Hospital and in association with the combined Cancer Clinic of the Chelsea Hospital for Women and the Royal Cancer Hospital bases his criteria of radioresistance on the effect of irradiation on mitosis as well as with its effect on surrounding connective tissue reaction. So far we have chosen to formulate the diagnosis of resistance on either clinical or biopsy evidence entirely.

Columnar Celled Carcinoma of the Cervix.—So far, in England, we have found these adenocarcinomatous growths very resistant. At the Chelsea Hospital for Women only 10 per cent survived over five years after radiation. Maliphant of Cardiff finds 14 per cent five-year survivals, and Professor Windeyer from the Middlesex Hospital reports about 14 per cent survivals. In a small personal series of eleven such cases which I have followed up after the Wertheim operation, so far four, or 36 per cent, are alive and well after a period of five years. In this respect also we have noted that the squamous endocervical growth appears more resistant than the more common exocervical growth.

The presence of large fibroids, ovarian tumors, or salpingitis in our opinion always contraindicates radiation, and all such cases are treated surgically if the patient's condition permits.

colleagues and I have decided to extend the practice of lymphadenectomy until such time as improvements in deep therapy or some other more effective method of treatment makes the procedure unjustifiable and unnecessary.

Technique of the Wertheim Operation.—It perhaps will interest you to outline a few of the technical modifications of the Wertheim Operation practiced in our hospital. Anesthesia is obtained by the use of intravenous pentothal followed by gas and oxygen combined with spinal analgesia using light percaïne intrathecal solution. Recently we have tried the use of gas, oxygen, and curare, but so far this has not proved popular. Most of us perform the lymphadenectomy early in the operation, immediately after making certain that the bladder can be satisfactorily displaced downwards. One of my colleagues, Aubrey Goodwin, practices lymphadenectomy early in the operation sweeping the glands medialwards and leaving the iliac and obturator lymph node chain attached to the uterus throughout. This early attack on the lymph glands facilitates early exposure of the ureters and uterine vessels, allows of better hemostasis, and has the psychological advantage in that it gives the surgeon a sense of completion as soon as the uterus with its attachments has been removed. I also have the impression that operative shock is somewhat lessened.

At least the upper one-half, and preferably the upper two-thirds of the vagina, are removed, and if this clearance be effected vaginal recurrence is almost unknown. The vaginal vault is left open for drainage purposes and the subperitoneal raw area is lightly packed with penicillin gauze, one end of which passes through the vagina. This gauze is removed in thirty-six hours. Plasma infusion or blood transfusion is practiced in every case as a routine, and the choice of solution depends upon the amount of blood lost.

The ureters and bladder are treated with the greatest gentleness and respect, and this is especially important in the post radiation cases. Over the past twelve years the incidence of postoperative urinary fistulas has been 3.1 per cent, a figure which compares favorably with that of fistulas following radiotherapy.

Conclusions

I trust that I have not given the impression that I do not appreciate the value of radiotherapy, but I do feel that there has lately been a tendency to take a broader view of the whole subject and to treat each case on its merits. In recent years radical surgery for the condition has tended to be underrated in its usefulness. The operative mortality in properly selected cases should not exceed 5 per cent, and should never reach the high figures sometimes quoted. The figures given for radiation always tend to favor that form of therapy, as the five-year results are always described as "survivals" and not as "cures." Indeed a large percentage of five-year radiation survivals are literally dying of cancer of attenuated virulence. The ten-year survival rate shows a very appreciable drop, and even after this time a considerable percentage of patients die of the remote sequelae of radiation. In following up these postradiation cases, the interpretation of thickening and infiltration is difficult to assess. The radium enthusiast calls this "fibrosis," the surgical enthusiast designates it as "recurrence" and the honest observer simply states that he does not know. After the Wertheim operation any thickening denotes recurrence, and the falling off in the figures of ten-year results is not nearly so great as in the case of radiation. Bonney estimates that between five and ten years he loses a further 10 per cent from recurrence.

radiotherapy are not due more to improvements in the details of application, screenage and dosage of the radium rather than to the addition of deep x-ray therapy. Indeed, the latest five-year report of the Holt Radium Institute in Manchester shows better results in Stage I and II growths with radium alone than with combined radium and deep x-rays.

However, their numbers are relatively small. One must confess that these results are at variance with those usually shown for other centers, but Dr. Pater-son of Manchester is unusually meticulous with his radium applications, and he certainly obtains the maximum intensity of radiation to the cervix and its neigh-boring structures from his vaginal radium application.

TABLE VII. RESULTS OF WERTHEIM'S OPERATION AT THE CHIEFSEA HOSPITAL FOR WOMEN FOR THE YEARS 1936 TO 1941, INCLUSIVE

| | STAGE I | STAGE II | STAGES I AND II |
|--|----------------|----------------|-----------------|
| Number of cases treated | 34 | 20 | 54 |
| Number alive at end of five years | 14-41 per cent | 10-50 per cent | 24-44 per cent |
| Lost in follow up | 5 | 1 | 6 |
| Number alive after five years excluding lost cases | 14-48 per cent | 10-53 per cent | 24-50 per cent |
| Operative deaths | | | 3 |
| Operative mortality | | | 5.5 per cent |

TABLE VIII. HOLT RADIUM INSTITUTE (MANCHESTER) 1945. CANCER OF CERVIX. 771 CASES. 1932 TO 1939
RADIUM TREATMENT WITH AND WITHOUT X-RAY THERAPY

| TECHNIQUE | STAGE I | | STAGE II | | STAGE III | | STAGE IV | |
|----------------------|---------|------------------|----------|------------------|-----------|------------------|----------|------------------|
| | NO. | 5-YEAR SURVIVALS | NO. | 5-YEAR SURVIVALS | NO. | 5-YEAR SURVIVALS | NO. | 5-YEAR SURVIVALS |
| A. Radium and x-rays | 23 | 62 per cent | 224 | 44 per cent | 212 | 29 per cent | 55 | 20 per cent |
| B. Radium alone | 35 | 76 per cent | 117 | 49 per cent | 58 | 25 per cent | 27 | 8 per cent |

In this respect also I have had some experience of performing lymphadenec-tomy after a full course of treatment by radium and deep x-rays. I have found a cured cervix with negative biopsy in association with positive lymph nodes apparently unaffected by the deep therapy. In all those cases (37) in which the lymph nodes have proved negative for carcinoma, they have been so mobile and so easily removed that I cannot believe that they have ever been involved. I have never yet removed adherent lymph nodes which have been obviously sterilized by radiation and which have been proved to be free of growth.

Likewise I have yet to see a recurrence following the Wertheim operation successfully treated by deep therapy, and this has also been Mr. Bonney's ex-perience.

We must accept the fact that in up to 80 per cent of Stage I growths the glands are unaffected, in up to 70 per cent of Stage II growths they are free, and in more than 50 per cent of Stage III growths there is no malignant in-volvement. Is it in these gland-free cases that the radiotherapist obtains his suc-cesses? No one will doubt that the adequate application of radium will cure the majority of the local cervical growths, but to my mind it is not yet proved how efficient is deep therapy in eradicating the disease from the glandbearing area. I feel with Dr. Taussig that there is a place for lymphadenectomy in selected Stage III cases which have been cured locally by radium, and I feel that such a procedure could well be extended to include Stage II cases and selected cases of Stage I growth. In such cases the operative mortality is negligible, and my

At this point Dr. Healy stated that they feel in cases of carcinoma of the cervix the important point, especially in advanced cases, is whether they are favorable for operative treatment or not, and that in their experience the end-result was in accordance with that. Continuing, Dr. Healy said:

"Dr. Read also mentioned that he finds they operate in about 14 per cent of their cases. That is remarkably interesting, and if I am not right about that he will correct me, because our figures show that those are the justifiable cases in which to operate. I think about 15 per cent of our cases at the Memorial Hospital as we examined them and classified them in the League of Nations group were regarded as very favorable cases in which you might consider surgical intervention and, of course, we were depending on radiation except where we met with radioresistant cases, and in those we always recommended surgery.

"I want to express my deep thanks to Dr. Read for his splendid presentation, with all of which I am in hearty agreement."

DR. HOWARD C. TAYLOR, JR.—"Like Dr. Healy I am impressed by Dr. Read's paper because he speaks from experience of a service reporting 600 or 700 cases, thus he has the advantage of an opinion which is predicated on the basis of a large experience. What strikes me, however, is that Dr. Read is making the opposite point here in New York from that which I think he perhaps intended to make. I gather that this paper was written, at least in part, to defend the position of surgery in the treatment of cancer of the cervix, and in his institution he has shown a great reduction from an operability of 63 per cent to 14 per cent. Consequently he comes to us, not as an apostle of surgery, but warning us against our present trend towards the extension of surgery. I may be wrong about that and may be putting words in his mouth, but I came here and received a totally different impression from what I expected as he pushed me in an entirely opposite direction from that which I anticipated.

"The question of what group to operate on and what group to assign to radiation is one which has received a great many different answers, and it is only with some difficulty that we can squeeze them into three or four different categories representing certain different schools of thought in relation to the indications for this disease. The first one is put into the surgical group, those which are extremely favorable from the standpoint of the extension of the disease. It is my impression that Meigs has done that because his operability runs about 10 per cent and includes, in general, the earliest cases. This grouping to me, seems illogical because he is changing the operability in that group of cases in which the results of radiation are the very best."

Citing the slide shown by Dr. Read from the Marie Curie Hospital, where radiation in Stage I carcinoma was as high as 80 per cent, Dr. Taylor stated that this means, if we are to consider the cure rate from radiation therapy to be 80 per cent in this category, that surgery would have to do better than 80 per cent. However, he said that, in his opinion, he did not think the cure rate in cancer will be much improved by changing the method of treatment, in 10 per cent of these particular cases, to radiation therapy. Continuing his discussion, Dr. Taylor said:

"Dr. Read has indicated a different method of selecting cases for operation, and those are the ones with very special indications, such as cases which appear to be radioresistant, and he wasn't quite sure whether he was able to judge radioresistance on the basis of type or the basis of preliminary x-ray treatment and trial of radiation therapy. In so far as that group is concerned, I would be very much interested in discussing it with the pathologist.

"In the second group of radioresistant cases the doctor presents special indications, such as the complication of pregnancy, stenosis of the vaginal vault, and one or two others. I think that type of selection is based on a very considerable degree of experience for the reason that that is a high degree of selectivity based on intuition and personal experience and with great difficulty reduced to statistical analysis. I would suggest that he will have difficulty in handling the material statistically in the future because, on the basis of selectivity, it will be extremely difficult to duplicate in other institutions.

Let me again stress that in my view in the present state of our knowledge the routine treatment of election for the average case of cancer of the cervix is by radiotherapeutic means, but that in certain selected cases there is a place for surgery which in these cases offers the best prospect for the patient. In addition I suggest that the more extensive practice of lymphadenectomy, especially in Stage III cases, might improve our results. It would at least enable us to assess the real value of deep therapy on the pelvic lymphatic glands if it were practiced as a routine after a course of such therapy. The pressing need at this moment is an investigation of 1000 consecutive lymphadenectomies after x-radiation.

I submit that the absolute cure rate in carcinoma of the cervix can be increased by a surgical approach to those cases which prove to be radioresistant or in which adequate radiation is not possible.

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Discussion

DR. WILLIAM P. HEALY.—“When talking about carcinoma of the cervix, Dr. Read speaks the same language that we do, and there is certainly no room, in my opinion, for destructive criticism of anything that the doctor has said, and constructive criticism is merely endorsement of the paper.

“I was very much interested in the slide in which Dr. Read referred to the indications for the Wertheim operation of hysterectomy. I think I might endorse all of it except possibly the final one about pregnancy as a complication of carcinoma, or carcinoma as a complication of pregnancy, but then Dr. Read has only had three cases which, of course, is not a very large percentage, so I won't discuss that because my colleague, Dr. Smith, has gone into that subject and is more competent to discuss it than I. However, with Item I I agree completely; it endorses all that we were teaching when I was at the Memorial Hospital as a reason for surgical interference in carcinoma of the cervix. We gave deep roentgen therapy first, and when the lesion in the cervix failed to show a response in ten or twelve days we knew we were dealing with a radioresistant lesion, clinically speaking, and, histologically, it could, of course, be demonstrated as readily. When the lesion, after apparently responding, breaks down and ulcerates again, you have a lesion which is not going to do well under radiation therapy.

“Then there is the third group. You may not cure those cases by operation, but you will at least cure the patient of the local recurrence with the persistent foul-smelling vaginal discharge and subsequent hemorrhage by doing a hysterectomy, and in a small percentage the patients will probably be cured.

Dr. Read very kindly showed in one slide the series of cases that I reported in 1930 or 1931, a total of 1,574 carcinomas of the cervix. That brings to my mind his second group of adenocarcinoma or columnar cell cancer of the cervix, in which he feels that there is a definite indication for hysterectomy. If my memory is correct, I reported 42 adenocarcinomas of the 1,574 cases, and the end-results in our series were not at all influenced by the histologic or the clinical setting of the case, and the advanced cases gave an equivalent percentage, clinically speaking. In other words, putting it this way, Stages I and II League of Nations and III and IV adenocarcinoma behaved exactly as the squamous cell.”

the distal nodes were also involved. That is my recollection. Clark improved in Wertheim's technique, but definitely thought it was not necessary to remove the glands if distal glands were involved. I would like to be corrected in that if I am wrong.

"In so far as radiation of the lymph nodes is concerned, Dr. Gusberg and I last year became interested in the technique of using interstitial radiation. One of the first things we tried to do was to ascertain how much radiation arrived at the lymph nodes by various technique as we know them from many studies; that of Nolan, for example, and my recollection is that it amounted to about one-half. So the question of radiation or sensitiveness to radiation of the lymph nodes is one in which I feel we should think of in terms of the lethal dose.

"Those are the only two points I have in mind (there is a possibility that I may be wrong): one, Wertheim's experience with lymph nodes, and, secondly, the fallacy of saying that the lymph nodes are not affected by radiation because as we studied them, they are affected."

DR. FRANK R. SMITH.—"No one could hear this delightful presentation without being impressed by Dr. Read's sincerity in the presentation of his facts, and I would like to thank him for it; I enjoyed every minute of it.

"You cannot help but be impressed by the futility of using percentage figures, especially where there is any selected material for the reason that there is human equation involved, and that differs where we use a clinical estimation of the stage of the disease, and that is one thing surgery has done in this disease; it has shown us how wrong we have been many times in our clinical estimation of the stage of the disease.

"I was interested in one of the slides the doctor showed in which it looked as if in surgery the more advanced the disease the better the results from lymphatic dissection.

"Dr. Smith then said that Stage I showed 41 per cent (of cures) and then changed it, as best could be understood, to 53 per cent for Stage I, or that figure for Stage II, and as far as Stage III was concerned, he said he forgot what that showed.

"I was also interested in Dr. Taylor's estimation of operability which is a good physiologic thought. Various people talk about operability, but it differs with different clinics. In this respect I was struck by Bonney's operability of 63 per cent as compared with Dr. Read's of 14 per cent. That is very interesting. It would also be of interest to know how many of his patients were radiated previous to operation, and whether they should be classified as primary operability or not. At Memorial Hospital we have no primary operability; all patients are radiated before operation.

"Before showing two slides, I would like to quote Dr. Kosmak and state that these are the opinions of the author and the Journal takes no responsibility for them.

"I simply present these slides to show the incidence of the various types of carcinoma, taking in Dr. Healy's regime in the first section, from 1922 to 1924. A, or Stage I, shows an increase, due perhaps to increasing publicity and better education of doctors; and B, or Stage II, shows an increase; Stage III diminishes, as would be expected, while Stage IV is about the same. In spite of improvement in material, we find pretty much of a plateau; that is, in recent years there has been a plateau in the results obtained by radiation. That was the reason we utilized the surgical approach to this disease at Memorial Hospital, to see if we could improve the cure rate. Now, if we take the two types Dr. Taylor so ably presented, the favorable operability, Stage I and II, and operated on them, giving them radiation at the same time and postoperative radiation, preliminary radiation being given at the present time by the vaginal cone, unless we appreciably improve our over-all statistics in those two groups, the question arises as to whether we are justified in putting the patient through a major surgical procedure as a substitute for the simple insertion of the radium pack. In other words, if our mortality is greatly increased, are we justified (in subjecting the patient to operation)?

"The second group is that in which there is a feeling of discouragement, in which we take the position that all we can do is palliate. In Stage III the salvage rate is low. In Stage IV we never have been able to do very much.

"In so far as salvaging cases in the third group is concerned, this is where we compare the value of surgery in respect to the second and third group and (in the latter group) the operability in this country is about 45 per cent." In group 3 Dr. Taylor observed that Dr. Read was predicating his opinion on the basis of his experience, which admittedly was not large, and added that, logically, he, personally, "always thought that operability should include those cases in which lymph nodes are involved, but capable of removal. That is the group in which, theoretically, surgery may cure a certain percentage of patients, whereas x-ray therapy will probably not cure any. It is doubtful whether radium in the cervix will reach the lymph nodes. Therefore, I think, on the basis of operability, we should not include the 10 per cent where only a very few lymph nodes are involved and there is a high percentage of radiation cures." Dr. Taylor now commented on the second and third group, which constitute a large number of cases, including those of the operable variety, without lymph node involvement, and stated that here is where you would expect a difference in the results between radiation and surgery, and that operability would vary between 40 and 50 per cent.

Continuing his discussion, Dr. Taylor said:

"The other point is, of course, increased operability with the Wertheim operation. We have not had enough experience with this procedure to speak with certainty, but I submit these different categories which may be considered in separating and evaluating the results between radiation and surgery.

"In closing, I am impressed that Dr. Read has reduced his operability to about 14 per cent. From the pathologic standpoint, however, I feel it should be around 40 per cent."

DR. GEORGE GRAY WARD.—"I am heartily in agreement with Dr. Read's general statements.

"The difficulty, of course, is that which we experience in determining Stage I, II, and III cases. For example, it is very hard always to know whether the infiltration that you may feel is inflammatory or carcinomatous. In some cases it is not possible to palpate the deep glands in the upper higher pelvis. Therefore, while apparently a case may be Stage I as you see it from below, it really may be further advanced from what you thought at firsthand.

"A group of us went abroad in 1912 and learned the technique of the operation from Wertheim, Franz, and Bumm, and other men who were doing this work in Germany, and on our return we practiced the operation here. In 1919 we abandoned it for radium. We have given six reports of our five-year salvage at the Woman's Hospital. Our first rate was something like 23 per cent total salvage. We have completed a seventh report, which has not as yet been published, and in this report in 217 cases our salvage rate is 35 per cent. This includes all cases, both early and late, and for the early cases, 61.5 per cent, which was quite a marked improvement over our first report. The primary mortality was 1.28 per cent. We had 15 cases in the series which were stump carcinoma cases, and we had some 46 per cent of cures.

"In the treatment of stump carcinoma Scheffey and Behney, of Philadelphia, as well as we, feel that the results in these cases are better than where the whole uterus is in place. Very often hysterectomy is done, leaving the cervix behind, and ultimately the patients develop cancer and these patients generally respond quite favorably to radiation.

"After all, the early cases are the ones requiring the Wertheim operation, but the average general surgeon or the average gynecologist is not trained in the technique of that operation, therefore radium undoubtedly will be relied upon in a great proportion of these cases, but there is no question that in the early cases, as Dr. Read says, the radical Wertheim operation or the extraperitoneal resection of the glands, or the Taussig operation, combined with radiation, will give better results."

DR. JAMES A. CORSCADEN.—"The adjective that comes to my mind is 'impressive.' This is a story of forty solid years in the study of this disease. I don't know of a similar study that has been carried on by any other group.

"There is only one technical point of interest to me and that is the matter of the lymph nodes. As I remember Wertheim's work, he dissected the glands and did a large number of serial sections of the glands and found when the regional lymph nodes were involved,

advent of antibiotics, chemotherapy, and blood transfusion the corrected mortality is about 5 per cent of all cases. Since the war we feel with the help of these adjuvants that the Wertheim operation is not one that carries with it such a high mortality and that it is capable of further improvement."

I feel that the Wertheim operation is one which involves teamwork and we like to use teams especially trained in its performance.

DR. NELSON B. SACKETT.—Referring to one of the main contentions of the proponents of surgery, Dr. Sackett stated that some years ago, at the Woman's Hospital, he studied about 900 cases, of which "359 were available for ten-year statistics. Without corrections for any cause whatsoever, the irreducible figures indicated that if a patient survived 5 years she would have a 75 per cent chance of being alive at the end of 10 years. A patient rarely died after surviving 10 years." This survey was made about 1937 upon cases who had received what is now considered inadequate primary radiation. With adequate irradiation five year survivors have over 85 per cent chance of living ten years or more.

"We have not been doing lymphadenectomy; but it should be done in cases where the local lesion has responded well."

Referring to the "criteria of Heymann, of Stockholm, or the League of Nations classification," Dr. Sackett stated that "where there is some doubt about the grouping of cases, they are always placed in the less advanced Stage."

In cases in which there is parametrial infiltration and one cannot decide whether it is malignant or not, if it clears up under radiation it is probably carcinoma; but if it fails to improve by this therapy or gets worse, it is probably inflammatory. That is a valuable point in determining the League of Nations stage.

After referring to one of the main contentions of the proponents of surgery, Dr. Sackett stated that some years ago, at the Woman's Hospital, he studied about 800 cases, of which "only 300 were available for ten-year statistics, and without any deductions or corrections for any cause whatsoever, the irreducible figures indicated that if a patient survived five years she would have well over a 75 per cent chance of being alive at the end of 10 years; that some died between five and ten years and a few died after the lapse of ten years." This survey was made about 1935, the doctor said, in the era of what is now known to be that of intractable primary radiation, as it sounded to the Reporter. Continuing his remarks, Dr. Sackett said:

"We have not been doing lymphadenectomy."

After a few further remarks, the doctor stated that their present figures indicate an increase in the survival rate in these cases if they were to eliminate intercurrent deaths, such as heart failure and various other causes, and that under these circumstances the survival rate would be well over 70 per cent and possibly close to 80 per cent.

Referring to the "criteria of Heymann, of Stockholm, or the League of Nations classification," Dr. Sackett stated that "where there is some doubt about the grouping of cases, they are always placed in the less advanced category."

After referring to two cases that they have in the hospital at the present time, both of which presented palpable glandular involvement, one of which it was possible to subject to preliminary x-ray therapy, and the other of which was not suitable for primary radiation, Dr. Sackett concluded his remarks as follows:

"Heymann states that in cases in which there is infiltration if one cannot decide whether it is malignant or not, if it clears up under radiation it is probably carcinoma, and if it fails of improvement by this therapy or gets worse, it is probably inflammatory. I think that is a valuable point in classifying these cases."

DR. WILLIAM CRAWFORD WHITE.—I have seen some of the ill-effects of irradiation. Moreover, I am very much interested in the fact that Dr. Taylor is talking about more and more surgery. I wonder how many cancer cells he is going to sweep around the peritoneal

"There is some justification in the so-called 'noble experiment' at Memorial Hospital. Today we attempt surgery for these people, but we must definitely ask ourselves the following questions: One, do we salvage appreciably any group of people who were not salvaged before? Secondly, do we make the patient more uncomfortable than we do with palliative radiation? Third, is the mortality much greater? Fourth, what is the time of palliation?

"I note that in Dr. Read's Stage III group, 22 patients, none lived eighteen months. Dr. Healy will tell you that we have had many of these advanced cases, so-called, clinically speaking, who have lived eighteen months or longer.

"If we are going to evaluate this so-called noble experiment, we must ask ourselves these questions.

"Since September 15 all patients with cancer of the cervix, whether they have Stage I, II, III, or IV, who have entered the wards of the Memorial Hospital have been treated surgically. There have been only three cases in which exploratory operation has been done. They had strange complications; one had deep metastasis in the liver, which is unusual, the second had complete involvement of the iliac vessels which infiltrated these particular structures, and the third had peripancreatic disease all around the upper abdomen." At this point, Dr. Smith referred to what sounded like "peritoneoscopy," which he said another man called "devisection, which I think is just as bad," and spoke of transplantation of the ureters along with other points of the technical procedure, the ureteral transplantation being done at the "same stage," and added that radium is left in the colostomy loop in these cases in which the rectum has been removed. "The over-all mortality," Dr. Smith remarked, "is 25 per cent of all patients." This mortality, however, the doctor said, could, if desired, be corrected, but the reporter was unable to get the corrected figure. "One patient died suddenly on the ninth day, I think, but no one knows what she died of. Up to that time she had been doing well. Even autopsy failed to disclose the cause of death."

At this juncture, reverting to a previous observation, Dr. Smith said, "Although it presents obvious danger, I still think it is a noble experiment. I am not speaking critically in respect to it, but it is surgical calisthenics unless it fulfills the qualifications I have stated. I do not believe we can talk about it until enough time has elapsed to show if it fulfills the qualifications. There is a bad effect about it. I think that many aspiring surgeons stand in some hero-worship of a great surgeon doing these colostomies. Very few hospitals, even in this city, are equipped to carry on such major surgery. These men watching the procedure and feeling that it is the recognized treatment of carcinoma of the cervix are going back to their suburban hospitals and attempt to do the operation, without being able to get sufficient blood while the patient is on the operating table. I think while it is a bad experiment, it is worthy of trial because it is done in unselected cases and the over-all figure will be an unqualified one."

DR. STENNING (Sydney, Australia).—Cancer of the cervix has been occupying our attention for a long time, and Dr. Slinck and Dr. Twig have been pioneers in doing the Wertheim operation at the hospital where I happen to be. I say that, actually, we feel our results in the treatment of carcinoma of the cervix compare favorably to those we have read about which have been reported in other parts of the world. They had been doing the Wertheim operation since 1927 and had already published a series of cases covering ten-year cures for the period 1930 to 1940, and it is anticipated that they will soon publish the fifteen-year cures.

"In our clinic we have always felt that it is rather difficult to estimate the stage of carcinoma and, furthermore, we feel that carcinoma should be subjected to radium treatment preliminarily and, if it then becomes favorable, to submit it to the Wertheim operation.

"We feel that by putting radium in at the beginning we take a lot of patients away from trouble because we find in some cases that the disease regresses. We don't rely entirely on what the outside world believes in regard to uterine cancer because we find some of them regress when we might have thought them radioresistant. We give the patients 7,200 milligram hours spread over a period of about five days, at the end of that time the radium is removed and then, five weeks later, if the patient is considered operable, operation is done. Prior to the war, the operative mortality was 15 per cent. Since the war period, however, with the

REVIEW OF THREE HUNDRED ANTERIOR AND POSTERIOR COLPORRHAPHIES*

With a Plea for an Anatomical Correction of These Traumatic Hernias Earlier
and With Presentation of Author's Procedures of Repair

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(From the Louisville General Hospital)

LACERATIONS of the perineum did not escape the notice of Celsus. The first repair procedure was based on the idea of reducing the size of the vaginal canal so that it would hold the uterus in place, but it was not until 1913 that Fothergill¹ published the details of his operation on correction of genital prolapse and for the first time gave an anatomical repair approach to the operation.

A review of the anatomic relationship is brought out in the following essays: Sears,² Hill,³ Davies,⁴ Goff,⁵ Barrett,⁷ Cameron.⁸⁻¹⁰

The pelvic structures are both suspended and supported. They are *suspended* by the ligamental folds of the peritoneum and fascia (round, uterosacral, uterovesical ligaments). They are *supported* by the pelvic diaphragm or the musculofascial floor of the pelvis (levator ani, and the perineal muscle group). They both support and complement each other and are situated one over the other in the pelvic strait.

Pelvic floor relaxations and the final result of complete prolapse of the uterus, the associated pelvic congestion, and pelvic structural changes, from beginning to end, vary only in degree, the process being essentially the same throughout.

Can we make the patient fit the operation as well as the operation fit the patient? If we are dealing with degrees of the same condition, we should strive to have a procedure that will anatomically suit the condition, and the indicated side procedures may be included at the same operative procedure. The one constant factor in all of these cases is the need for an anatomical repair of the cystocele and rectocele, which is least stressed or in some cases almost forgotten in many of the approved operative procedures. Great stress is placed on the technique of the vaginal hysterectomy and the interposition operations, but little or no emphasis is placed on the anatomical repair of the hernia,^{11, 12} in the anterior and posterior walls of the vagina. Without a good foundation, how long can an architectural masterpiece stand? We are not only dealing with different

*Read before the Central Association of Obstetricians and Gynecologists, on Oct. 25, 1917, Louisville, Ky.

cavity (unwittingly, of course) when he does that operation. Objectively, I think it is a factor that most of us are not fully aware of. I have definitely demonstrated in breast surgery that there are plenty of cancer cells in the washings from our gloves after operation. I believe there are many cells which are distributed about in the wound at the time of operation. I think that must be borne in mind (in considering surgery) versus radiation where there is a great deal of fibrous encystment and retardation of growth.

"There is another factor which I do not understand, but which, nevertheless, is a factor, and that is, when there is metastasis it may lie dormant for varying periods of time; then something happens which causes the cells to grow again. Therefore, as long as the patient lives she may start to grow cancer again. I know that in my personal experience I have seen patients who have lived, thirteen, fifteen, and even seventeen years and at the end of that time start to grow cancer again, despite the fact that they had been in perfect health in the interval.

DR. READ (Closing).—"My first thought, I frankly admit, was that I would be hung, drawn, and quartered by the deep x-ray therapists because I thought I might provoke some discussion on their part or, rather some disagreement with the views I advanced, and I find that such an exponent of this method of treatment as Dr. Corscaden has more or less agreed that x-ray radiation does not adequately radiate the pelvic lymph nodes.

"I was interested in Dr. Healy's statement that in his hands adenocarcinoma cases showed almost as good results as the squamous celled group. However, that has not been our experience. Whether we are faulty in our technic of radium application or not I cannot say, but I do not think that any clinic in England which has taken the trouble to analyze the adenocarcinoma cases and contrast them with squamous epitheliomas, show any results comparable to those obtained by radiation in the squamous celled group.

"To Dr. Taylor I would say that a large number of people would probably prefer operative interference to the exclusion of every other means of treatment, but it must be remembered that this evolution in our Hospital has come about after having had extensive experience with the radical operation as a routine method of treatment in all cases. In respect of operative possibilities in Stage III cases you cannot get away from the fact that the clearance in Stage III cases is not a very wide one." This is borne out by the results, and as expected the surgical results are worse in Stage III than in Stages I and II cases. You cannot escape the fact that Stages I and II growths give the best results radiotherapeutically, so I feel until some better results are shown by surgery it is best to be conservative and treat these cases radiotherapeutically except in those instances in which radioresistance is proved, and that is an important point.

"Radioresistant cases fall into three classes: one, where the cervix fails to heal; two, where it heals and then later breaks down and thirdly where at a still later date biopsy shows persistence of continuous activity. When I speak of repeated biopsies I refer to instances of radioresistance where active growth is shown three, four or six months later; that is, active growth present in the cervix three months or six months later. In one of my cases active growth was present 14 months after radiation.

"I agree with the difficulty of classification. As a matter of fact, about 60 per cent of my lymphnode dissections resulted from misinterpretation of the type of disease with which I was dealing. I remove the appendages in these cases in which the lymph nodes are extirpated and it is from such cases that I obtain the greater proportion of material.

"Dr. Corscaden mentioned the question of remote gland involvement. That is an important and interesting point. I did not mention it here, but for years in those of Mr. Bonney's cases subjected to the radical operation and who died, at autopsy, it was remarkably rare that remote nodes were found in cases that were clinically operable. Some are found in the region of the celiac axis vessels but, generally speaking, in the Wertheim operation a complete gland clearance begins at the bifurcation of the aorta, and if this is free you can skin the glands completely from the bifurcation downwards. It is not always the case that remote glands are not involved and I can cite two cases of clinically Stage I growths with metastatic involvement of the supraclavicular gland group.

In respect to Dr. Smith's discussion, I think there is some slight mistake on Dr. Smith's interpretation of what I said. In 45 of the 54 patients who were subjected to operation there was proved radioresistance, and these were doomed to death because biopsy showed active growth with break-down of the initially-healed cervix. The remaining 9, a small proportion, came into the groups I mentioned, such as pregnancy, stenosis of the vaginal vault, and the others conformed to the other categories.

"I agree with Dr. Taylor on the question of the advanced growth. It is a difficult problem, and a matter of conscience on the part of the surgeon. Whether he does ultraradical surgery involving cystectomy or partial colectomy in addition to radical hysterectomy depends on the attitude of the patient herself. In other words, if the growth is so advanced that you cannot effect a cure radiotherapeutically and the alternative is certain death, certain patients will say, 'I leave it to your judgment.' The results can only be assessed on the basis of a large number of cases and, as far as I know, this has not been done. But there is the other factor: Is the patient more comfortable after extremely radical surgery than she is following radiation? I cannot answer that question for the reason that I have not had a sufficiently large experience of such cases.

"It was interesting to hear Dr. Stenning of Sydney, Australia, say that they are still doing the Wertheim operation as the method of selection. Actually, if you work it out over a series of figures, you will find that, roughly, 30 to 31 per cent of all patients presenting are alive at the end of five years whether treated by radiation or by surgery. I think if you combine surgery with radiation, in selected cases, you can get that survival rate up.

"I am not enough of a mathematical genius to figure out what Dr. Sackett had in mind, but as I understood him he said that when a patient lives five years after radiation she has a 75 per cent chance of living five years longer and a 25 per cent chance of dying within the next 5 years."

NEWER CONCEPTS OF MENSTRUATION*

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BLEEDING is the most striking feature of the menstrual process. A large part of the clinical and laboratory study of menstruation in the past two decades has, therefore, been directed toward the blood vessels of the endometrium. On the basis of this work, an explanation of cyclic uterine bleeding as a consequence of alterations of the coiled arterioles of the endometrium has gained widespread acceptance. Unfortunately, this explanation has been carried so far that it now fits only certain special cases. The most recent laboratory findings as well as many familiar clinical observations require a return to a more general physiologic concept of menstruation as a result of withdrawal of metabolic support of the endometrium.

It has been known for some time that the vasculature of the endometrium undergoes cyclic changes along with the glands and stroma (Saito,²² Daron⁵). The basal arterioles, situated in the deepest portion of the endometrium, are not shed in the menstrual discharge and do not participate in these cyclic changes. The coiled arterioles, which eventually reach almost to the superficial epithelium, manifest remarkable alterations. Just after the completion of bleeding, the endometrium is shallow and the coiled arterioles have but a few loops. As the follicular phase proceeds, the endometrium thickens and the arterioles add loops and lengthen, remaining confined to the inner half of the mucous membrane. If ovulation fails to occur and growth continues, due to continued estrogen stimulation, vessels such as those in Figs. 1, 6, and 7 develop. If, however, a functioning corpus luteum is formed, the coiled arterioles become much more complex and extend further out into the endometrium as the secretory changes of the glands and stroma take place. With the approach of menstruation, the contortion and buckling of the vessels become extreme, as in Figs. 2, 8, and 9. The distal portion of the vessel is lost thereafter in the menstrual discharge. Markee¹⁵ has added greatly to the understanding of these changes by describing them as they take place in endometrium transplanted to the anterior chamber of a rhesus monkey's eye. He observed that the bulk of endometrial bleeding is arteriolar in origin and that, therefore, the coiled arterioles control the amount and rate of menstrual hemorrhage. The explanation of menstruation as a consequence of vascular changes is based primarily on these observations.

In the years that have followed the publication of these findings, so many interpretations of their meaning, all of them similar, have been made in textbook and monograph discussions of menstruation that it would be unfair to cite any one author's exposition of the vascular hypothesis. It is restated here without citation, therefore, in its two basic forms, with the awareness that the separation between them is academic.

*Presented before the Obstetrical and Gynecological Section of the Baltimore City Medical Society, Feb. 13, 1948.

The first, a mechanical concept, is based on the observations that the coiled arterioles increase rapidly in complexity and extent as the secretory phase of the cycle progresses. This increasing complexity is supposed to reach a point at which it impedes the flow of blood to the endometrium, producing ischemia,

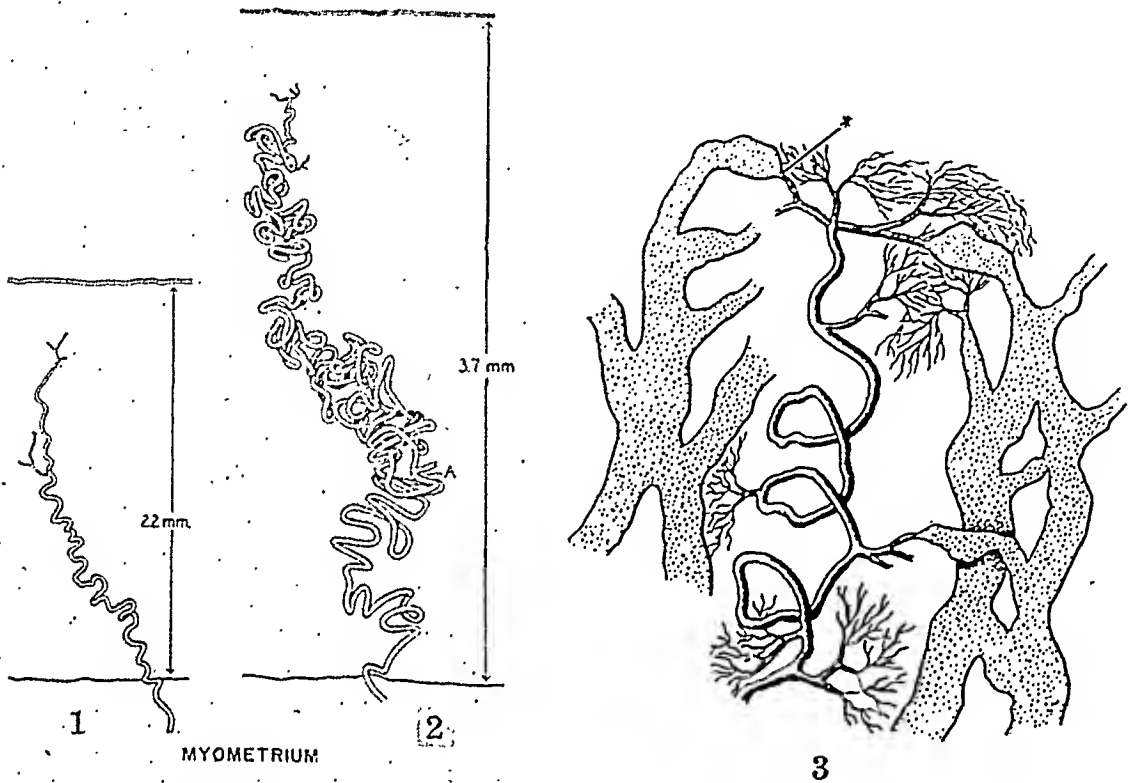


Fig. 1.—Projection reconstruction ($\times 20$) of the lumen of a coiled arteriole on the twenty-sixth day of an anovulatory cycle. One ovary contained a large cystic follicle. By this stage the vessel of an anovulatory cycle is usually more complex than this, as may be seen in Figs. 6 and 7. The simplicity of this vessel, as compared with that in Fig. 2, is striking and somewhat overstates the ease. Reproduced from Daron, *Am. J. Anat.* 58:405, 1936, Fig. 9.

Fig. 2.—Projection reconstruction ($\times 20$) of the lumen of a coiled arteriole on the thirtieth day of an ovulatory cycle. Branching occurs at A but only one branch has been reconstructed. Note the complexity of this vessel and compare with Figs. 8 and 9, which illustrates a similar vessel, on the first day of menstruation. The contrast with Fig. 1 requires no comment. Reproduced from Daron, *Am. J. Anat.* 58:403, 1936, Fig. 5.

Fig. 3.—Schlegel's sketch of endometrial vasculature of the human uterus as seen in injected material. The coiled arteriole ascends between two large columns of veins. At the asterisk and at two other places arteriovenous anastomoses are indicated. This is a highly diagrammatic representation. Reproduced from Schlegel, *Nord. Med.* 24: 2061, 1947, Fig. 2.

which then sets off the chain reaction of menstruation. The other, a pharmacodynamic concept, stems from the observation that prolonged periods of vasoconstriction are invariable precursors of the other menstrual changes. The growth and differentiation of the coiled arterioles are presumed to render them sensitive to the action of vasomotor substances. These then produce vasoconstriction, ischemia, and menstruation. Both concepts assume that continued growth of a complex coiled arteriole is a necessary precursor of menstruation. In this sense, the hypothesis of a vascular basis of menstruation as stated by many authors, compounded freely of ideas from both of the concepts stated

above, bypasses and even contradicts the earlier work on hormone withdrawal as the common precursor of menstrual flow. As will be discussed below, such a conclusion is quite erroneous.

A new factor in this vascular explanation has been introduced by the recent observations of arteriovenous anastomoses in human endometrium.

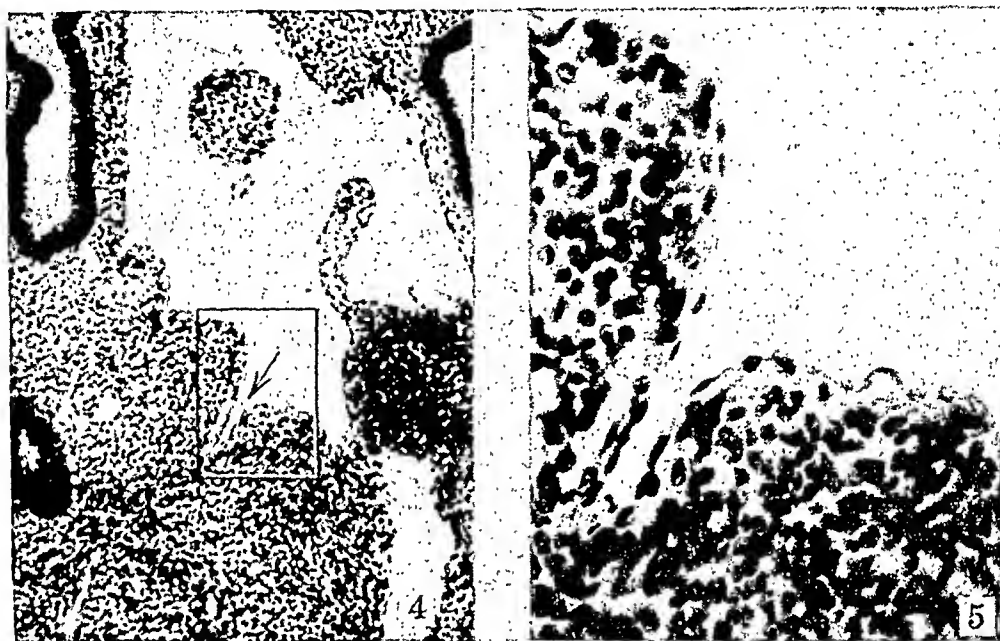


Fig. 4.—Section of human endometrium ($\times 90$). A large venous lake and several glands may be seen. At the arrow, an arteriole enters the venous lake. Reproduced from Schlegel, *Nord. Med.* 24: 2067, 1947, Fig. 10.

Fig. 5.—Detail of Fig. 4 ($\times 360$). At this magnification, the identification of the vessel entering the venous lake is by no means as definite as at the lower magnification, although some detail is undoubtedly lost in photography. Reproduced from Schlegel, *Nord. Med.* 24: 2066, 1947, Fig. 9.

Dalgaard⁴ and Schlegel²³ have independently reported the presence of shunts between the branches of coiled arterioles and venous lakes of the functional zone. As described by Daron,⁶ these venous lakes are dilated venules which appear shortly before menstruation in the middle third of the endometrium. Schlegel's sketch of these vessels is reproduced in Fig. 3. His first observation of anastomoses was made in human uteri injected with colored substances under high pressures. Under the microscope, after sectioning the uteri, Schlegel was able to see points where his red arterial injection mass met the blue venous material without the intervention of a capillary bed. Dalgaard, who injected India ink into the arteries, found large numbers of ink particles in the venous lakes. Both authors were later able to find the anastomoses in uninjected histologic preparations. One such anastomosis is shown in Figs. 4 and 5, which are made from Schlegel's original photographs. Schlegel and Dalgaard agree that these shunts occur with increased frequency in the secretory phase of the menstrual cycle. Schlegel suggests that eventually so much of the arterial blood is shunted into the venous system that a capillary ischemia results. This then precipitates endometrial breakdown and menstruation. He also argues that the presence of arteriovenous anastomoses provides an ideal vasculature for the establishment of placental circulation.

The existence of these shunts cannot be accepted without reservations. Bartelmez¹ has reported his inability to find anastomoses in the endometrium of the rhesus monkey, but this may be a species difference. The very high pressures employed by Schlegel and Dalgaard for injection raise a question about the production of artefacts. It is certainly difficult to make a positive identification of so small a vessel as that seen in Figs. 4 and 5 as arteriolar. Serial sections of endometrium are required to prove the presence of these arteriovenous anastomoses conclusively. Nevertheless, the fact that these structures have been observed independently by two workers makes subsequent confirmation appear likely. Sehlegel²⁴ has recently reported clinical studies of the effect of ephedrine on dysmenorrhea, based upon the possible vasomotor action of this drug on the arteriovenous anastomoses.

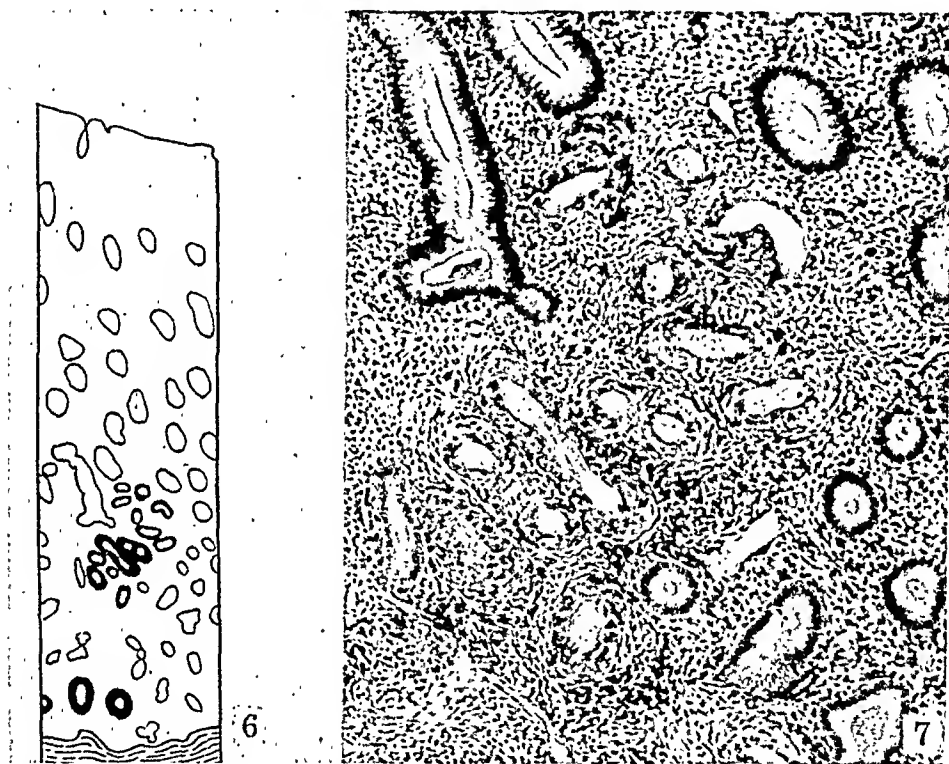


Fig. 6.—Outline drawing of a section of endometrium of the rhesus monkey ($\times 25$) on the twenty-eighth day of an anovulatory cycle. This and Fig. 8 were made by printing photographs of these sections and then drawing in the outlines of the superficial epithelium, glands and arterioles. The myometrium was sketched in schematically. The photograph was then bleached out. The arteriolar field is restricted to the inner half of the endometrium and is relatively simple as compared with Fig. 8. Reproduced from Kaiser, *Anat. Rec.* 99: 215, 1947, Fig. 6, with changes.

Fig. 7.—Photograph of the arteriolar field in Fig. 6 ($\times 100$). The vessel walls are compact and eosinophilic. Reproduced from Kaiser, *Anat. Rec.* 99: 221, 1947, Fig. 14.

It is difficult to explain the amenorrhea of early pregnancy by the current hypothesis of a vascular mechanism for the initiation of menstruation. Although no special study has been devoted to this matter, it appears reasonable to assume that the coiled arterioles of the endometrium in the relatively vast area removed from the site of implantation differentiate to the same extent as those of the nonpregnant uterus, at least in the first fourteen days after ovulation. The same assumption may be made in reference to arteriovenous anastomoses.

Nevertheless, bleeding does not usually occur in the pregnant animal. Schlegel attempts to account for this by postulating a special local effect of chorionic gonadotropin which increases the "irrigation coefficient" of the capillary bed and thus prevents anoxemia.

There are still other objections to the vascular explanation. It has been repeatedly observed that the coiled arterioles found in the presence of ovulatory menstruation differ considerably from those seen during anovulatory bleeding.¹² Despite this fact, the clinically observed bleeding is identical in the two conditions by all our present criteria. The major differences in the appearance of coiled arterioles of the rhesus monkey in these two circumstances are shown in Figs. 1, 2, 6, 7, 8, and 9. Figs. 6 and 7 depict the typical appearance of a coiled arteriole on the twenty-eighth day of an anovulatory cycle. They demonstrate maximum anovulatory growth. In contrast, Figs. 8 and 9 show the vessels

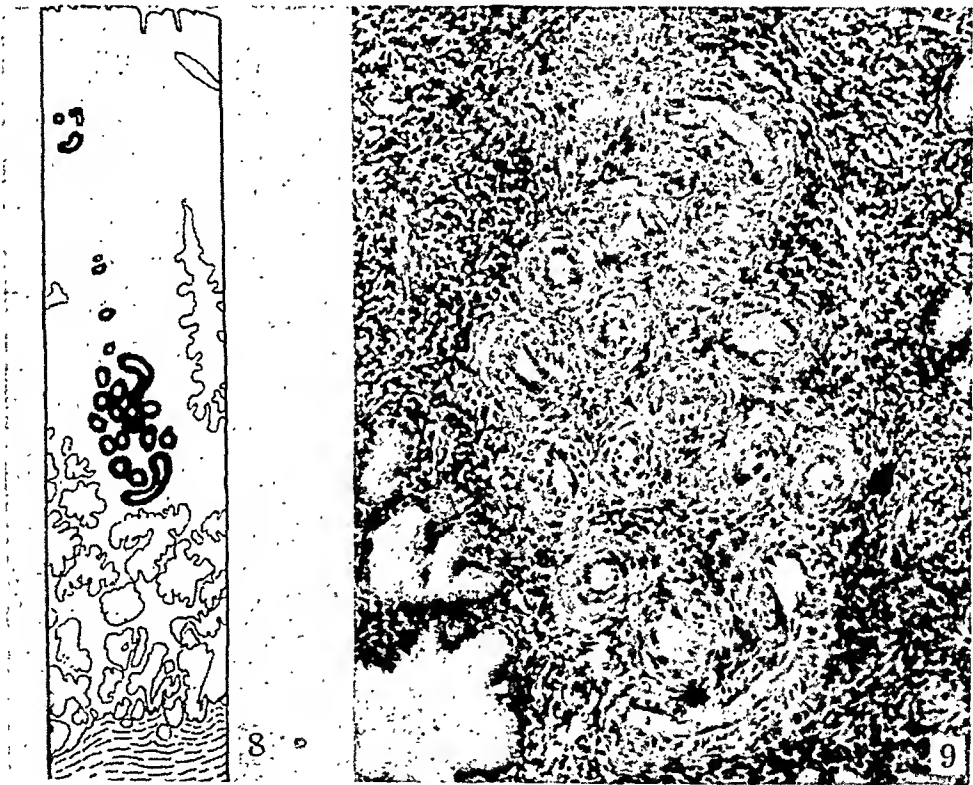


Fig. 8.—Outline drawing of a section of endometrium of the rhesus monkey ($\times 25$) on the first day of ovulatory menstruation. The arteriolar field is in the middle of the endometrium and branches are seen extending well out toward the superficial epithelium. The field is more complex than in Fig. 6. Reproduced from Kaiser, *Anat. Rec.* 99: 215, 1947, Fig. 1.

Fig. 9.—Photograph of the arteriolar field in Fig. 8 ($\times 100$). The arteriolar walls are swollen and much less eosinophilic than these in Fig. 7. Reproduced from Kaiser, *Anat. Rec.* 99: 217, 1947, Fig. 9.

in the endometrium at the onset of menstruation in an ovulatory cycle. Comparing Figs. 1 and 2, and 4 and 6, it can be seen that the vessel of ovulatory menstruation is larger, more complex, and reaches further out toward the superficial epithelium. Its area of greatest coiling is in the middle third of the endometrium. In Figs. 7 and 9, higher magnification reveals that the vessel walls in ovulatory cycles are thicker and stain less deeply. These differences

are known to be an effect of progesterone. Detailed studies with cytochemical techniques are required to prove their functional significance. It must be remembered that bleeding can and does occur from an endometrium with a much simpler arteriolar bed than these. Such is the case in bleeding following oophorectomy or spinal cord transection done at the midinterval, for example. Although no study has been made of this subject, coiled arterioles are not conspicuous in the presence of endometrial hyperplasia, despite the bleeding with which this condition is associated. Finally, there is suggestive evidence that bleeding can occur in the rhesus monkey under experimental conditions without any proliferation of coiled arterioles at all (Kaiser¹⁴).

Menstruation, at least in the form of microscopic cyclic bleeding in the absence of coiled arterioles, has recently been shown by Kaiser¹⁵ to be the normal condition in the New World monkeys. These animals, which are closely related anthropologically to the other Simiæ, including the rhesus monkey and man, were long believed not to menstruate. However, more detailed studies by Goodman and Wislocki,⁸ and Hamlett,⁹ using daily vaginal lavage, have revealed cyclic uterine bleeding of microscopic proportions in the New World species. The endometrium of these platyrrhine monkeys goes through a cycle much like that of the rhesus and the human being (Dempsey⁷). Despite this, a special study of the vasculature of the platyrrhine endometrium has demonstrated that there are no coiled arterioles present. Instead, there is a very simple system of small arterioles which run through the endometrium almost without contortion after branching once or twice in the basalis. These vessels do not appear to undergo any cyclic alterations. Two of them may be seen at the arrows in Fig. 10. This illustration depicts the appearance of ovulatory menstruation in the endometrium of a capuchin monkey. The contrast between the arterioles in Figs. 7 and 9 and those in Fig. 10 does not require emphasis.

These observations indicate that the current explanation of menstruation based upon alterations of the coiled arterioles fails to account for much that is known about the menstrual process. Before a vascular explanation can be abandoned, more information is needed concerning the contraction cones described by Daron.⁵ He pointed out that the arcuate arteries of the myometrium traverse the muscle parallel to the serosal surface and give rise to the radial arteries which run at right angles to it. These then travel toward the uterine cavity and divide into two types of vessels. One type enters the endometrium to become a basal arteriole, the other to become a coiled arteriole. In several menstruating uteri, Daron observed that the radial arteries which led to coiled arterioles are constricted so as to form a cone of contraction in the zone of myometrium adjacent to the endometrium. This may be seen strikingly in Fig. 11, from Daron's original preparation. It is clear that such a constriction would effectively occlude the blood supply of the endometrium. Okkels and Engle¹⁶ and Hasner,¹⁰ who have described the microscopic structure of the myometrial radial arteries and their branches have unfortunately not discussed this phenomenon. Indeed, Okkels and Engle appear to describe contractile tissue only in the walls of the basal arterioles. If, however, there are structures

capable of occluding blood supply to the vessels which supply the spongiosa and functionalis, then a simple vascular explanation of menstruation may be possible regardless of the presence or absence of coiled arterioles.

It may be noted here that the sole study of lymphatic channels of the endometrium of the rhesus monkey has indicated that lymphatics are absent from the spongiosa and functionalis.²⁷ Hence menstruation may be in part due to an inadequate mechanism for the resorption of tissue breakdown products following the cessation of metabolic support. Reynolds²¹ has recently discussed this matter in more detail.

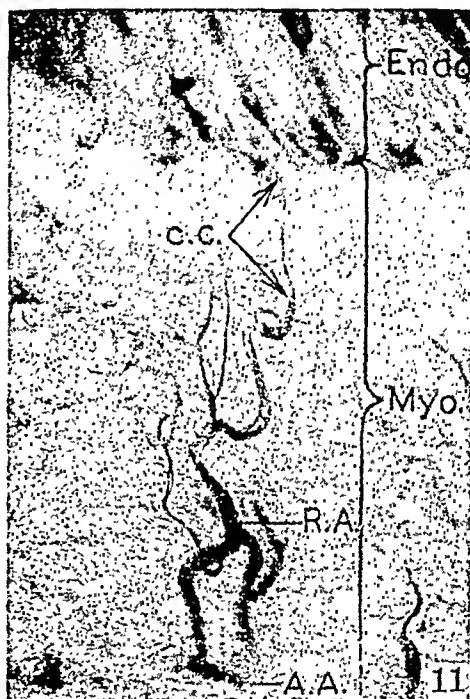


Fig. 10.—The endometrium of a menstruating capuchin monkey ($\times 40$). There is disorganized debris in the lumen with a large amount of leucocytic infiltration but not much destruction of the epithelium. The more superficial glands manifest evidence of progestational changes. Two medium-sized arterioles (c. 40-50 microns) are seen at the arrow. Reproduced from Kaiser, Anat. Rec. 99: 367, 1947, Fig. 4.

Fig. 11.—Photograph ($\times 34$) of a cross section, 0.2 mm. thick, of the uterus of a rhesus monkey on the second day of the menstrual phase of an anovulatory cycle. The myometrial arcuate artery (A.A.) in the vascular stratum of the myometrium (Myo) gives rise to a myometrial radial artery (R.A.). This vessel in turn enters the endometrium (Endo) at the arrow, to form a coiled arteriole. In the inner fifth of the myometrium, the radial artery is tightly constricted. This is the contraction cone (C.C.) of Daron. This is a previously unpublished photograph of material from Daron's animal No. 113.

Influence of Past Cycles on Endometrium

A most significant contribution to the understanding of abnormalities of menstruation has recently been made by Phelps as a culmination of a series of studies^{3, 17, 18, 19} in the Department of Obstetrics and Gynecology of Vanderbilt University Medical School. These have followed the observation by Zuckerman²⁸ that the effect of a single dose of estrogen on the monkey is affected by its response to and distance in time from previous estrogen stimulation. Phelps¹⁹ has now directed attention to the factor of previous treatment in the production of menstrual disorders in the rhesus monkey. She states that:

"... any given episode of uterine bleeding is . . . influenced by the components, relative strength and duration of action of hormonal stimuli acting prior to application of the current stimulus. In other words, the influence of a single course of stimulation by ovarian hormones is not limited to the cycle which that course of stimulation represents. Its influence extends through at least one subsequent cycle and probably through more than one. This influence upon subsequent cycles is mediated at least in part through the structural changes produced in the endometrial vascular bed. These changes may be transient or permanent, i.e. carried over into

has an important influence upon the duration of the uterine bleeding in that cycle."

It is evident from this that to function normally the epithelium, stroma, and blood vessels must develop simultaneously to the same level of functional capacity. It is not enough that the epithelium alone develops. Hertig's essay¹¹ on the endometrium during the human cycle unfortunately does not include sufficiently correlated reference to the arterioles. A correlated study of endometrium and arterioles throughout the cycle in the human being would provide a base line with which the endometria of abnormal reproductive cycles could be compared.

It has long been assumed that if the ovary forms a corpus luteum, all the necessary events for successful implantation inevitably follow. There is, however, little reason to assume that every corpus luteum which forms reaches the level of hormone production necessary for the coordinated growth of all endometrial structures. Certainly there must on occasion be a failure to form a functioning corpus luteum. Under these circumstances, endometrial growth, and the growth of coiled arterioles in those species in which they are present, does not proceed to its fullest extent. This, in turn, as Phelps emphasizes, sets the stage for further endometrial anomalies in later cycles. Brewer and Jones,² discussing corpus luteum-endometrium relationships, point out that there is considerable variation, especially at the end of the cycle. They report one case in which an apparently normal corpus luteum was associated with endometrium which showed no evidence of past or present secretory activity. They surmise that this reflects either failure of the corpus luteum to function or failure of the endometrium to respond. They also point out that these variations are quite common.

The observation of the activity of endometrial epithelium on one occasion, or the determination of hormone levels in one cycle would, therefore, appear to be only the start of a thorough investigation of menstrual abnormalities. Before a therapeutic regime directed at the correction of infertility on the basis of menstrual abnormalities can be declared a success, all the elements of the endometrium, the epithelium, the stroma, and the blood vessels, must have returned to normal. At present, it can be suggested that certain kinds of in-coordinate growth of these three elements may be related to certain types of functional abnormality. If this be the case, endometrial biopsy should prove to be of increasing value as an index of therapy.

Discussion

Menstruation is but one phase of a continually varying cycle of growth and regression. It is the period of return to a resting condition of an endometrium

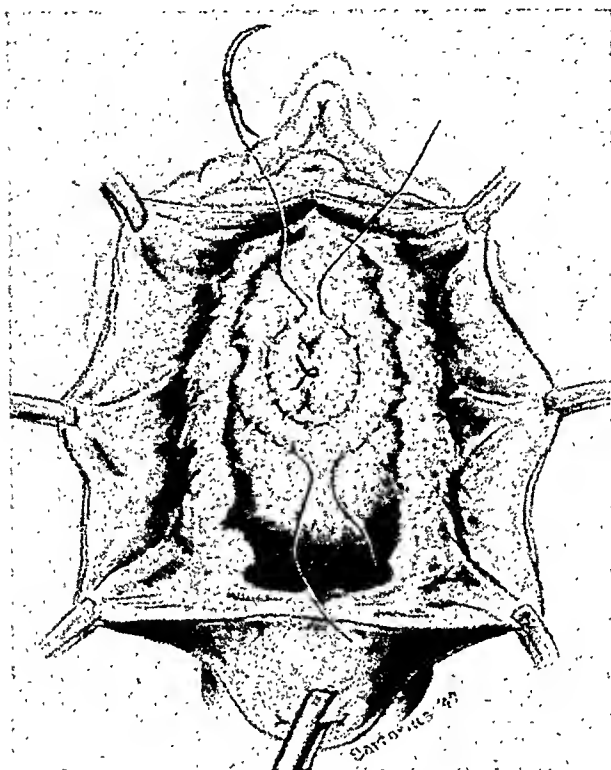


Fig. 1.—Attachment of bladder to cervix has been cut. Bladder is being advanced beneath the pubovesical fascia by purse-string sutures.

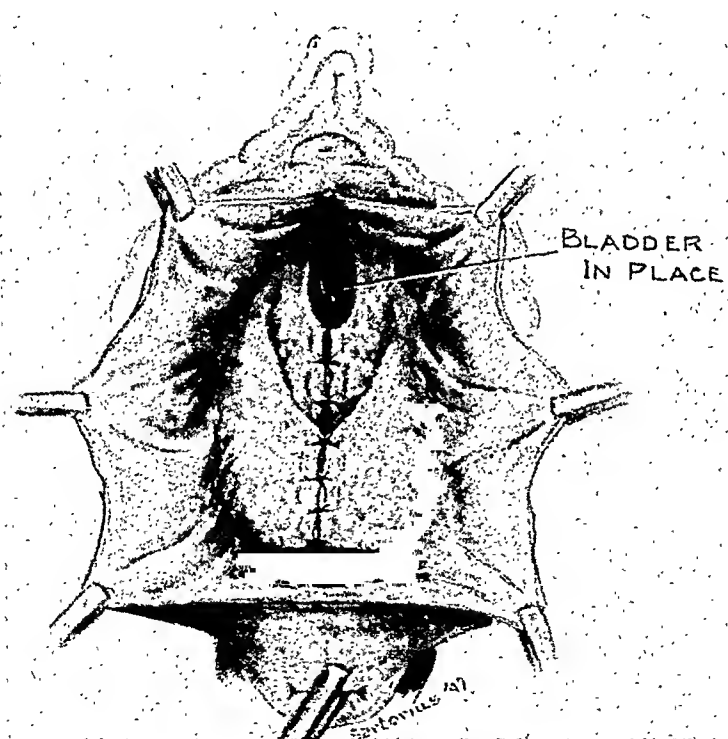


Fig. 2.—Bladder replaced in proper position. Sutures have been placed for approximation of pubovesical cervical fascia beneath bladder and to the anterior wall of the internal os of the uterus.

the catabolites formed following withdrawal of metabolic support. They remain in situ and cause further tissue destruction until the endometrium is shed down to the area maintained by the capillary bed of basal arterioles.

The other major clue is Markee's observation¹⁵ that regression in the rhesus monkey is not necessarily followed by menstruation provided that it proceeds slowly. By withdrawing estrogens gradually over a long period of time, he was able to produce transition from full growth to a resting state without necrosis, hemorrhage, or desquamation. The factor of time is, therefore, of crucial importance. The mechanisms for resorption which do exist in the primate endometrium do not operate with sufficient speed to prevent an accumulation of toxic substances which is lethal to the tissue itself. This aspect of the problem of menstruation has received but a fraction of the study it deserves.

It is unlikely that the coiled arterioles play any significant role in these basic events. Kaiser has described the absence of such vessels in the endometrium of menstruating New World monkeys. He has also observed their almost complete absence in the endometrium of rhesus monkeys which have received massive doses of estrogens. Other animals given the same doses manifested uterine bleeding upon withdrawal of the hormone. Finally, it has been repeatedly observed in the maeaque that there are no differences in uterine bleeding between ovulatory and anovulatory cycles. The major differences between the coiled arterioles in these two kinds of cycles have been discussed. This does not refute Markee's conclusion that, when present, these arterioles act to regulate the extent of hemorrhage. Nevertheless, menstrual bleeding occurs whether coiled arterioles are complex, simple, or absent altogether.

It seems much more likely that the coiled arteriole is of principal importance in the process of implantation of the embryo. The evidence for this is as yet only indirect. Ramsey has made a beginning in her study of the changes of the endometrial vasculature during pregnancy in the rhesus monkey.²⁰ Phelps has produced evidence that menstrual irregularities are associated with anomalous growth of the coiled arterioles in rhesus. This may therefore offer further explanation of the relative sterility of women with menstrual irregularities. Phelps' other observation, that the effects of hormone administration are dependent at least in part on the previous hormonal history of the subject as reflected in the state of the coiled arterioles, has very broad implications in the study of sterility. Some of these have been suggested. The further investigation of the association of the coiled arterioles with the implantation of the fertilized ovum, especially in the light of this anamnestic vascular phenomenon described by Phelps, can be expected to yield results of great experimental and clinical interest.

The author wishes to thank Dr. Garman H. Daron of the University of Oklahoma and Dr. Jorgen U. Schlegel of the University of Copenhagen for their generosity in lending their original materials for reproduction in this paper. The publishers of *Nordisk Medicin*, the *Anatomical Record*, the *American Journal of Anatomy* and the *South African Journal of Medical Sciences* generously gave permission for reproduction of figures which originally appeared in their publications.

which has undergone a period of growth. Once endometrial growth has occurred, a steady supply of metabolites, increased over that required for the resting state, must be maintained if regression is to be prevented. Further, the metabolites must be supplied in ever increasing quantities if continued growth is to occur. The steroid sex hormones provide the growth stimulus to the endometrium and thereby regulate its metabolic needs and participate in its metabolic support. When metabolic support is withdrawn, regression begins. This statement is true for all mammals.

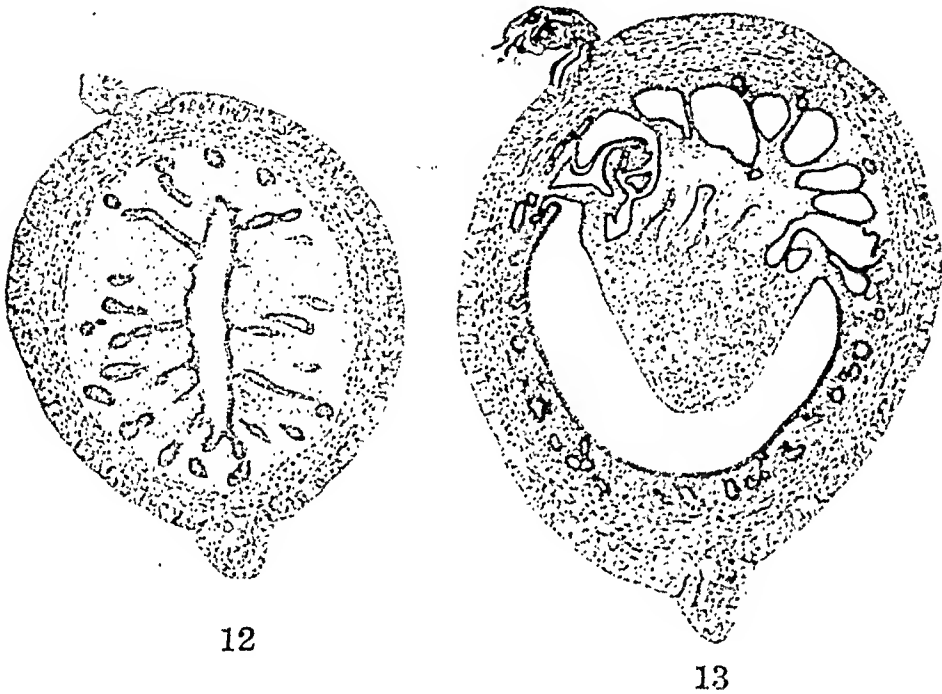


Fig. 12.—Transverse section of a uterine horn of the South African elephant shrew, *Elephantulus myurus* ($\times 25$). This animal has recently ovulated. The mesometrial border is at the top. The two layers of myometrium can be readily made out. The glands and stroma are uniform in appearance throughout the circumference of the horn. Reproduced from van der Horst and Gillman, South African J. M. Sc. 6: 1911, Fig. 3.

Fig. 13.—Transverse section of a uterine horn ($\times 25$) of the elephant shrew showing a large endometrial polyp. This is the normal state when ovulation is not followed by implantation. The polyp always develops on the mesometrial side. The uterine glands beneath it are dilated, while those elsewhere are small. The stroma away from the polyp is dense and compact, while between the polyp and the dilated glands remnants of stromal edema can be seen. The polyp itself has undergone necrosis, although the covering epithelium is still intact as a very thin layer not visible at this magnification. It is immediately following this stage that bleeding occurs from the necrotic area. Reproduced from van der Horst and Gillman, South African J. M. Sc. 6: 1911, Fig. 12.

Why, then, do only certain primates menstruate? There are two major clues to an answer. Van der Horst and Gilman^{27, 28} have observed cyclic uterine bleeding in the South African elephant shrew which is classed by most taxonomists as a rodent. The endometrium of this animal responds to progesterone by forming a large endometrial polyp, almost a deciduoma. This polyp grows until, at the end of the cycle, it undergoes necrosis, hemorrhage, and desquamation. This may be seen in Figs. 12 and 13. It appears that this remarkable growth exceeds the capacity of the uterus for resorption of tissue and tissue-breakdown products. This is in all likelihood also true of the primate endometrium. There are no lymphatic channels present to provide ready egress for

LEIOMYOSARCOMA OF THE UTERUS*

Report of 16 Cases, 1917 to 1948

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A RECENT unusual incidence of leiomyosarcoma of the uterus (four case specimens in six and one-half months) observed in our pathologic laboratory has stimulated interest in reviewing the cases of this unusual neoplasm. Unhappily, the correct diagnosis is rarely made, or even considered, at the operating table due to the low incidence and the extreme difficulty in gross pathologic diagnosis. At the Methodist Hospital, we were able to find only 16 clear-cut cases of leiomyosarcoma in a thirty-year survey ranging from Jan. 1, 1917, to Jan. 1, 1948. During this same period, 2,318 benign leiomyomas and 40,382 general pathologic case specimens were examined. The ratio of leiomyosarcomas to leiomyomas was approximately 1 in 145, or 0.69 per cent, and to the general specimens 1 in 2,524, or 0.04 per cent.

TABLE I. INCIDENCE OF SARCOMA UTERI

| | SARCOMAS | LEIOMYOMAS | INCIDENCE (PER CENT) |
|---------------------------------|----------|------------|-------------------------|
| Evans ⁷ | 13 | 3,297 | 0.39 |
| Pemberton ¹² | 14 | 2,991 | 0.46 |
| Meigs ¹⁰ | 9 | 1,330 | 0.68 |
| Novak and Anderson ¹ | 59 | 6,981 | 0.84 |
| Kelly and Cullen ¹³ | 17 | 1,400 | 1.2 |
| Kimbrough ² | 43 | 3,338 | 1.3 |
| Bosse and Stanton ⁶ | 27 | not given | "approximately 2.0" |
| Davis, Howe, and French | 16 | 2,318 | 0.69 |

Table I shows that our percentage incidence of leiomyosarcomas to leiomyomas is comparable to the rate in other larger series of uterine sarcoma. It is of note that our group contained no instances of endometrial sarcoma, or sarcoma botryoides.

In the last twelve months of this study we have segregated the cellular leiomyomas from the usual type. Twenty-five of 223 leiomyomas, approximately 1 in 9, were found to be in this category, an incidence of 11.2 percent.

We have tried to analyze this 16 case series from a clinical, operative and pathological point of view with an eye to clarifying, as far as possible, the criteria for diagnosis at the operating table and under the microscope. The survival rate is correlated with the operative procedure, the degree of malignancy, and the recurrence incidence found in each case. Two general

*Read, by invitation; at a meeting of the New York Obstetrical Society, Oct. 14, 1947.

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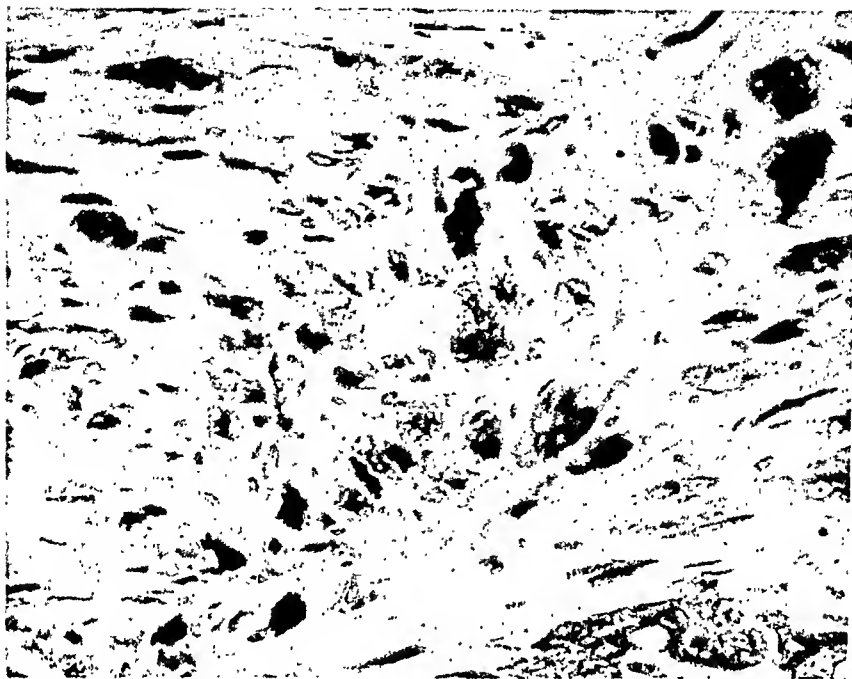


Fig. 1.—Case No. 5, unequivocal leiomyosarcoma, Grade 4, marked pleomorphism with numerous tumor giant cells is a striking feature. Hematoxylin and eosin, $\times 370$.

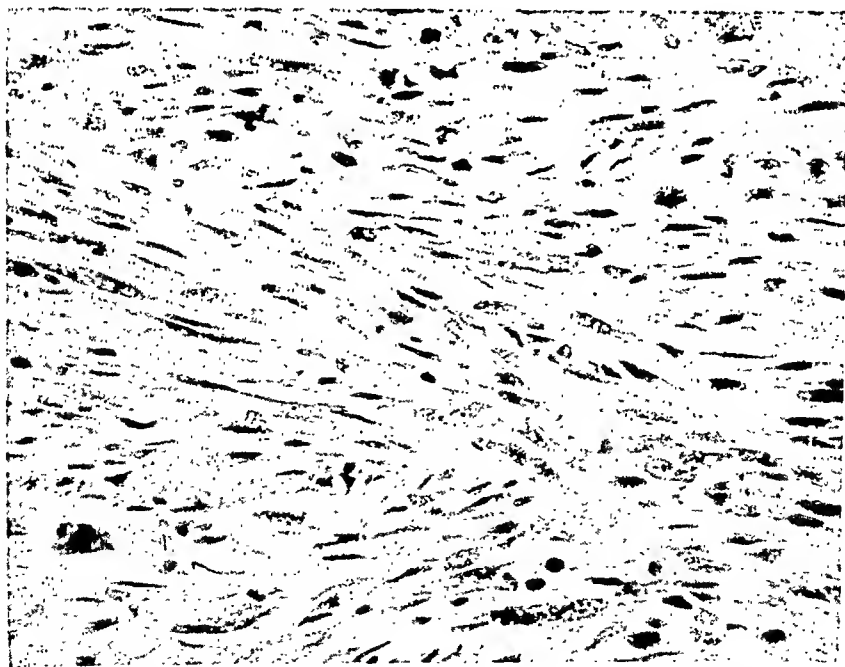


Fig. 2.—Case No. 4, unequivocal leiomyosarcoma, grade 3, characterized by moderate pleomorphism, numerous mitotic figures, and a moderate number of tumor giant cells. Hematoxylin and eosin, $\times 370$.

grades of malignancy are noted: the first, unequivocal leiomyosarcoma, and the second, low-grade leiomyosarcoma.

Gross Criteria.—The gross characteristics of the tumors as detailed in the operative notes and the pathologic descriptions were analyzed, particularly with relation to distinguishing them from leiomyomas. The results are shown in Table II.

TABLE II. GROSS APPEARANCE OF LEIOMYOSARCOMAS (16 CASES)

| | NO. OF CASES |
|--|--------------|
| Grossly indistinguishable from leiomyoma | 2 |
| Consistency different from leiomyoma | 14 |
| A. Soft and necrotic | 11 |
| B. Friable and granular | 3 |
| Color different from leiomyoma | 7 |
| Loss of fasciculation | 10 |
| Gross evidence of invasiveness | 2 |

From Table II, it appears that in 14 of the 16 cases there were gross characteristics of the tumor which might help to distinguish it from the common leiomyoma. It is true that degenerated leiomyomas may show similar changes. In most of our cases, the unusual appearance of the tumor at operation was incorrectly attributed to degeneration of a leiomyoma.

Leiomyosarcoma has been classified grossly into two types: (1) sarcoma arising in pre-existent leiomyoma, the so-called "sarcomatous degeneration of a fibroid"; (2) primary sarcoma arising in the myometrium. In some cases, there may be great difficulty in deciding this point. Primary sarcomas may be nodular and may occur in association with leiomyomas. In an advanced case, it may be impossible to reconstruct the origin. As might be expected, the incidence of the two types shows considerable variation when we compare the series reported. Novak and Anderson¹ cite 39 to 50 cases, or 78 per cent, as developing in myomas. Kimbrough² gives 26 to 43 cases, or 60 per cent, as secondary. Wheelock and Warren³ classify 32 of 35 cases, or 91 per cent, as arising in leiomyomas. In our series, 14 of 16 cases, or 88 per cent, were classified grossly as arising in leiomyomas, a figure which agrees more nearly with that of Wheelock and Warren than with those of the other authors cited.

Histologic Criteria.—The literature reveals a considerable difference of opinion concerning the histologic criteria for the diagnosis of leiomyosarcoma. Corseaden and Stout⁴ take the somewhat pessimistic view that none of the histologic criteria are reliable, and insist on evidence of infiltration, metastasis or recurrence as the only valid evidence of malignancy. McFarland⁵ similarly states that metastasis is the only proof of malignancy. Bosse and Stanton⁶ believe that gross or microscopic evidence of invasiveness is the most reliable criterion of malignancy. Other authors, however, have found good correlation between histologic criteria and the degree of clinical malignancy. Evans,⁷ and Novak and Anderson¹ classified their cases of leiomyosarcoma on the basis of mitosis counts and found that the degree of mitotic activity rather closely paralleled the clinical malignancy. Proper and Simpson⁸ classified their series of cases into three groups according to the degree of immaturity of their cells, and found that this paralleled the degree of clinical malignancy. Recently Wheelock and Warren³ analyzed their series of 35 cases, using twenty histologic criteria of malignancy. On this basis, they distinguished three grades of sarcoma. Grades 2 and 3 they considered clinically malignant, while grade 1 was considered clinically benign.

It is apparent that the varying histologic criteria account to a considerable extent for the disagreement in statistics on the incidence of leiomyosarcoma, as well as on the survival rates. Thus, Foot³ states that "leiomyosarcoma is more academically than actually malignant, and rarely metastasizes." However, Novak and Anderson¹ report a five-year survival rate of 30 per cent in their series of 59 cases, which included all types of uterine sarcoma. Kimbrough² cites a comparable figure of 34.3 per cent of five-year survivals in his series of 43 cases.

We have studied our cases histologically, according to the following criteria:

1. Cellularity
2. Anaplasia (degree of cell immaturity)
3. Pleomorphism (variation in cells)
4. Relative frequency of tumor giant cells
5. Relative frequency of mitotic figures
6. Invasiveness

Histologic invasiveness, while a valuable criterion of malignancy when present, was of little use in our series, since it was present in only 2 of 16 cases.

Each case was rated on each of these criteria on a scale of 1 plus to 4 plus. By averaging these values, a histologic grade was assigned to the tumor. The rating was done on representative sections and as objectively as possible, although it is recognized that there is an inescapable subjective factor in any such grading.

On further analysis of the four grades of tumors, it became apparent that they fell readily into two main groups. The first of these, comprising grades 3 and 4, showed to a considerable degree the classical histologic features of malignancy, and for this group we propose the term unequivocal sarcoma. The diagnosis of sarcoma in this group would probably cause little disagreement among pathologists, except for those who insist on invasiveness, recurrence, or metastasis as evidence of malignancy. It is interesting that originally one of these, Case No. 4, was diagnosed as "probable sarcomatous degeneration of a leiomyoma." Another, Case No. 10, was diagnosed as "marked degeneration of a fibroid." On re-examination, the few better preserved areas showed unequivocal sarcoma, although most of the tumor was too necrotic for satisfactory diagnosis.

The second group, comprising grades 1 and 2, showed less striking evidence of malignancy and would doubtless cause considerable disagreement among pathologists as to diagnosis and prognosis. On the basis of this series, we feel that tumors in this group cannot be dismissed as clinically benign, but may show a tendency to local invasion and recurrence, although perhaps not to metastasis. For this group we propose the term low grade leiomyosarcoma.

A third group of cellular, but benign leiomyomas, we have purposely excluded from this study. This comprised a fairly numerous group (approximately 11 per cent of leiomyomas) in which the tumor was unusually cellular, and some of which showed as many as 10 mitotic figures per high power field. However, the cells were uniform and mature.

Clinical Data.—An analysis of the age range, symptoms, and signs is given in Table III.

The patients in this series were all white; 9 were nulliparous, 6 multiparous, and 1 unknown. The average age was 47.2 years, with a range of 34 to 73 years. The greatest incidence, 10 cases, was found in the 40 to 50 year period. The major symptoms are noted above. Only six patients were aware of an enlarging pelvic or abdominal mass, although in all 16 pelvic examination revealed a readily palpable tumor. It must be remembered that

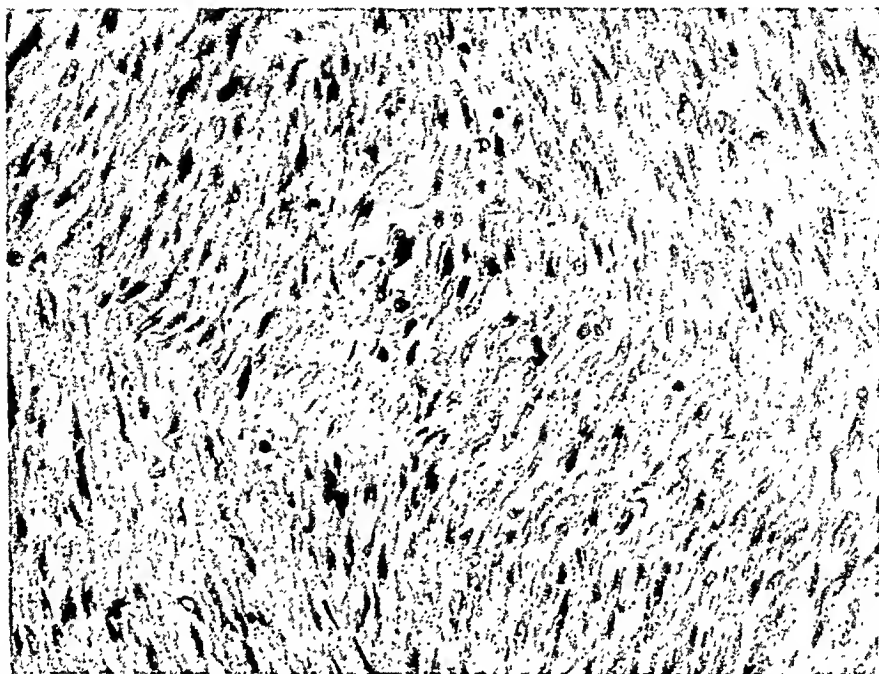


Fig. 3.—Case No. 11, low grade leiomyosarcoma, grade 1. The cells are moderately immature and occasional giant cells and mitotic figures are seen. Hematoxylin and eosin, $\times 370$.

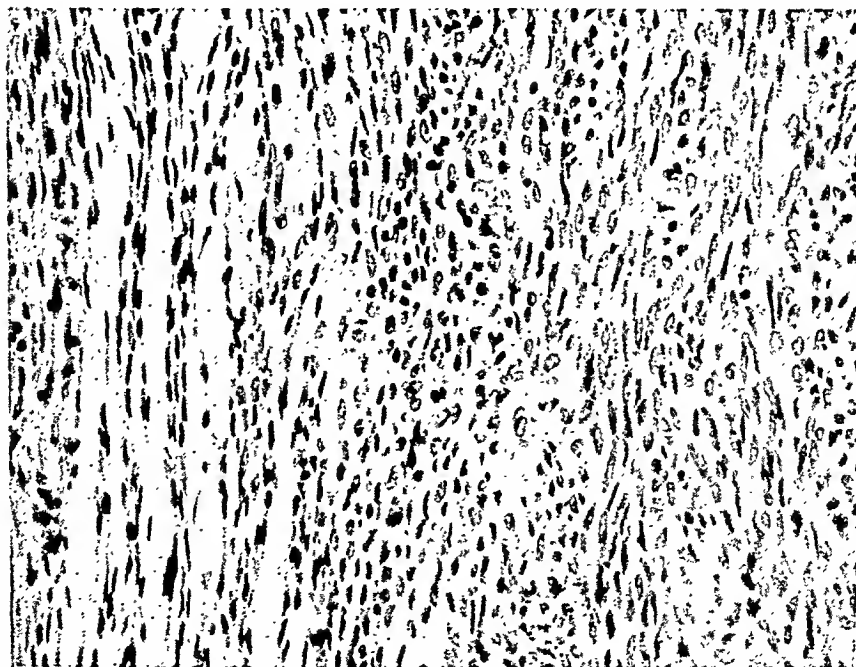


Fig. 4.—Cellular benign leiomyoma. Note maturity and uniformity of cells. Hematoxylin and eosin, $\times 370$.

equivocal. The postoperative period of each is brief, one and one-twelfth and three and three-fourths years, and obviously one can draw no conclusions as yet as to recurrence or final outcome.

TABLE VI. PATIENTS ALIVE WITH RECURRENCE

| CASE NO. | AGE | SOURCE | GRADE OF LEIOMYOSARCOMA | OPERATION | RECURRENCE |
|----------|-----|-----------|-------------------------|---|---|
| 6 | 42 | Leiomyoma | Unequivocal | Total hysterectomy Bil. sal-oophor. (prior curettage) | Hemi-colectomy for sarcoma. mass terminal ileum at 4 1/6 yrs. Living to date 4 1/2 yrs. |
| 11 | 48 | Leiomyoma | Low-grade | Subt. hysterectomy Bil. sal-oophor. Appendectomy | Exc. 2 omental sarcoma masses at 6 5/6 yrs. Living to date 7 2/3 yrs. |

In case 6 the diagnosis of leiomyosarcoma was made by curettage, and the complete operative procedure was dictated by the laboratory diagnosis. There were no omental nor small bowel adhesions at the time of hysterectomy. Recurrence at four and one-sixth years of sarcoma in the terminal ileum was diagnosed by x-ray following a four months history of asthenia, anorexia, severe anemia terminating in "bloody stools." We interpret this recurrence as a blood stream metastasis of an unequivocal sarcoma. Surgical exploration revealed no pelvic or abdominal recurrence; exhaustive x-ray studies have been negative. The patient is well at 4 1/2 years, but the prognosis is very guarded due to the grade of the sarcoma (unequivocal), and the possibility of other undemonstrated metastases. Case 11 is interesting in that the initial tumor mass was a pedunculated leiomyoma, the source of the low-grade leiomyosarcoma. We were not able to substantiate the presence of omental adhesions, which we suspect may have been present. We can only say that six and five-sixth years after the initial operative procedure, two discrete omental leiomyosarcomatous masses were removed; again the pelvis and the remainder of the abdominal cavity revealed no recurrence. The patient is living and well over nine months after her recurrence and seven and two-thirds years after her initial operation.

In both the above cases the recurrent tumors were identical in structure with the primary uterine sarcomas. Furthermore, the smooth muscle origin of the recurrent sarcomas was proved by their characteristic staining reaction with Masson's stain.

Table VII shows that all deaths were cases of unequivocal sarcoma, and each case reveals evidence of spread based on autopsy, operative, or x-ray findings. Case 1 revealed the entire uterus to be a mass of leiomyosarcoma. Direct and lymphatic extension had occurred to the bladder, right tube and ovary, left adrenal, retroperitoneal lymph nodes, gastrocolic omentum, peripelvic and sacral lymph nodes; there was an associated fibrinopurulent peritonitis. Case 4 was characteristic of spread by blood stream. Autopsy revealed no local pelvic lesions or involved glands, but there were distant metastatic lesions in the lungs and right auricle. Case 9 showed a huge inoperable pelvic mass, the size of a five months' gestation, with marked bowel invasion, probably a spread by both contiguity and lymphatics, in the opinion of the operator. Fractional x-ray was given with no apparent effect. Autopsy was not obtained. Case 10 was an example of amputation of the uterus through a portion of the tumor with apparent pelvic spilling. Seven months later exploratory laparotomy revealed the pelvis filled with an inoperable tumor mass; biopsy was

symptoms are often produced by, or are relative to, the associated leiomyomas and accurate differentiation is difficult. Five cases revealed a severe anemia, the hemoglobin range being 5.9 Gm. to 10.3 Gm.

TABLE III. CLINICAL DATA

| | |
|---------------------------|----|
| Total No. Cases | 16 |
| 30-40 years | 2 |
| 40-50 years | 10 |
| 50-60 years | 2 |
| 60-70 years | 1 |
| 70-75 years | 1 |
| <i>Symptoms and Signs</i> | |
| Menorrhagia | 8 |
| Metrorrhagia | 4 |
| Postmenopausal bleeding | 3 |
| Abdominal pain | 3 |
| Watery diarrhea | 3 |
| Weight loss | 2 |
| Enlarging mass | 6 |
| Severe anemia | 5 |

Tables IV through VII give a detailed analysis of the cases, including the pertinent pathologic data, the operative procedures, and the results.

TABLE IV. 1917-1948

| | |
|------------------------|-------|
| Total Number of Cases | 16 |
| No Follow-up | 3 |
| Inadequate Follow-up | 2 |
| Alive to date | 5 |
| Without recurrence | 3 |
| With recurrence | 2 |
| Deaths | 6 |
| Autopsies | 2 |
| Mortality Rate (known) | 54.5% |
| Survival (known) | 45.5% |

In the following discussion we have considered only those cases in which the outcome is known to date. Two of our cases had follow-up examinations at nine months and one and one-half years, respectively, but both have been excluded because no further follow-up has been obtainable in many years. In Table V is noted our small group of three patients living and well to date without recurrence.

It is interesting but not conclusive that our two patients above who had subtotal hysterectomies have to date shown no pelvic recurrence. The site of origin in each case was a fundal leiomyosarcoma and each was graded as un-

TABLE V. PATIENTS ALIVE WITHOUT RECURRENCE

| CASE NO. | AGE | SOURCE | GRADE OF LEIOMYOSARCOMA | OPERATION | FOLLOW-UP |
|----------|-----|--------------------------------|-------------------------|--|-------------|
| 2 | 44 | Leiomyoma (Fundal) | Unequivocal | Subt. hysterectomy Lt. Sal.-oophorectomy Rep. femoral hernia | 1 1/12 yrs. |
| 3 | 40 | Leiomyoma (Fundal) | Low-grade | Total hysterectomy Bil. sal.-oophor. | 1 1/6 yrs. |
| 5 | 44 | Uterine wall (Fundal, diffuse) | Unequivocal | Subt. hysterectomy | 3 3/4 yrs. |

degrees of the same condition, but with different individuals which necessitates individualization of the problem, and the procedures used should be considered along the following lines:

1. The age and general physical condition of the patient.
2. Desirability of preserving menstruation.
3. Desirability of preserving child-bearing functions.
4. Degree of descensus and condition of supporting structures.
5. The co-existence of disease of the cervix or corpus uteri.
6. The size of cystocele and rectocele and condition of repairability of supporting structures.
7. Previous operative work.
8. "Will" of the patient to co-operate and get well.

These conditions of prolapse and descensus are not all due to "poor obstetrics," or "bad obstetrical judgment," nor to "obstetrical neglect." In many women there is an inherent defect in the development of the muscle and fascial structures that support the uterus and other pelvic and generative organs, which predisposes them to develop these debilitating conditions, as is found in the following:

1. Late onset of menstruation with persistent retroversion of uterus in constitutionally inferior women.
2. Borderline or infantile pelvic organs before their first pregnancies, followed by retroversion after pregnancies.
3. Effects of frequently repeated labors.
4. Atrophy and loss of tissue tone and elasticity incident to menopause.
5. Spina bifida occulta.
6. Traumas from tumors and other causes leave the pelvic floor and its faulty attachments unable to withstand the forces of the frequent excessive strain of coughing, sneezing, and straining with stool, etc., until all the supportive structures give way and complete prolapse results.

These unfortunate women are like the poor, "always with us." The patient is interested only in the relief of her symptoms and not in a differential diagnosis. With an insertion of properly fitted pessary, clearing up of vaginitis, relieving the congestion and teaching the patient better care of herself, she soon finds that she is on the road to improvement of her symptoms, if not a complete cure, and she must be prepared mentally as well as physiologically for the operative procedure.

We wish to present an analysis of three hundred such individuals, taking 196 charity cases from the Louisville General Hospital, the operation being in most instances supervised by the author in the training of the House Staff, and 104 private cases between 1938 and 1942. In this group there were only three Negro patients. Two hundred ninety-four of the cases were multiparous, and five charity cases and one private case were nulliparous. All of these cases had moderate to severe cystocele and rectocele and no third degree tears.

TABLE VII. DEATHS

| CASE NO. | AGE | SOURCE | GRADE OF LEIOMYO-SARCOMA | OPERATION | SURVIVAL | AUTOPSY |
|----------|-----|-------------------------|---------------------------------------|--|--------------------------------------|---|
| 1 | 73 | Uterus (in-determinate) | Unequivocal | Inoperable: Biopsy of tumor | 2½ mos. | Sarcoma in uterus, rt. tube, ovary, bladder, omentum, etc. |
| 4 | 42 | Leiomyoma (Fundal) | Unequivocal | Subtotal hysterectomy, Bil. sal.-oophor. Appendectomy | 16 mos. | Metastatic sarcoma of lungs and rt. auricle |
| 9 | 46 | Leiomyoma | Unequivocal | Inoperable: Biopsy of tumor | 3 mos. (died in hospital) | No autopsy. Inop. sarcoma invading bowel |
| 10 | 46 | Leiomyoma | Unequivocal (with de-gen. & necrosis) | Subtotal hysterectomy | 9 mo. (died at home) | No autopsy. Expl. operation, Biopsy implant. on pelvic peritoneum at 7 mos. |
| 12 | 34 | Leiomyoma (Fundal) | Unequivocal | Subtotal hysterectomy, Lt. sal.-oophor. | 2½ yrs. (died at home) | No autopsy. Pulmonary metastases by X-ray at 2 yrs. |
| 14 | 51 | Leiomyoma | Unequivocal | (1) Myomectomy (vaginal) with drainage (2) Subtotal hysterectomy (6 wks. after above) | 6 plus weeks (died 2 d. post-op.) | No autopsy "Masses in sigmoid and omentum" |

made of an implant on the pelvic peritoneum. Death at home followed in two months. Case 12 showed spread via the blood stream to the lungs, demonstrated by x-ray. Death occurred at home nine months after x-ray studies, and no autopsy was obtained. The local doctor believed "there was no pelvic or abdominal recurrence" but this opinion was unsubstantiated by reliable examination or autopsy in Case 14. Sarcoma was first diagnosed after vaginal excision of a submucous leiomyoma. Laparotomy six weeks later was apparently a heroic attempt to remove a large uterine sarcomatous mass. Great difficulty was experienced in control of bleeding, and the patient died on the second postoperative day. No autopsy was obtained.

Discussion

We believe that leiomyosarcoma can be diagnosed with reasonable accuracy from histologic criteria. A division into two grades seems justifiable, and for these we propose the terms "unequivocal leiomyosarcoma" and "low grade leiomyosarcoma."

The gross appearance of 14 of our 16 cases differed from that of an ordinary leiomyoma. However, these could be easily confused with a degenerated leiomyoma. We would suggest that any leiomyomas which are unusually soft, friable, or of unusual color should be viewed with suspicion and incised, after removal, at the operating table. Immediate consultation with the pathologist, with frozen section examination when necessary, may establish the correct diagnosis and permit the proper complete surgical procedure to be performed. In the absence of such consultation, the gynecologist should con-

sider the advisability of performing a more radical procedure when he encounters grossly atypical leiomyomas or those with a history of rapid growth, particularly in the age group over 40 years.

It is suggested that at operation the omentum, if adherent to leiomyomas, should be widely excised. In one of our cases recurrence in the omentum occurred six and five-sixth years after hysterectomy for a low grade sarcoma.

In one case of our series, local and pelvic implantations occurred within seven months, following incision through a supposed "degenerated leiomyoma" in the course of a subtotal hysterectomy. This illustrates the danger of a too-limited surgical approach, creating a pelvic spill of the tumor. To date, this is the only early case in our series showing cervical or pelvic recurrence. As a further point in surgical approach, it is suggested that traction on the round ligaments or adnexa is safer than tenaculum traction on a leiomyomatous uterus, to avoid clearing a friable leiomyosarcoma with possible resultant spill of tumor particles.

In our series, the most common type of sarcoma (14 of 16 cases) was that arising in a leiomyoma. In this group, we have observed metastasis by blood stream, and by direct extension. In one case demonstrating lymphatic metastasis, the exact site of origin in the uterus was indeterminate.

Our series suggests that leiomyosarcoma arising in the fundus rarely recurs in a retained cervical stump, providing the site of excision is well below the involved area. In spite of this we feel that total hysterectomy with bilateral salpingo-oophorectomy, when the operative status of the patient warrants it, is the procedure of choice.

Summary

1. Sixteen cases of leiomyosarcoma of the uterus occurring in a thirty-year period at the Methodist Hospital, Brooklyn, New York, are reviewed.
2. Histologic criteria are suggested for classifying these under two types, unequivocal leiomyosarcoma and low grade leiomyosarcoma.
3. The unequivocal leiomyosarcomas tend to metastasize widely, as well as to implant locally.
4. The low grade leiomyosarcomas may recur in contiguous structures after relatively long periods.
5. Of 16 cases, 11 had adequate follow-up. Of these, six, or 54.5 per cent, died of metastases within two and three-fourths years. Three cases are living and well, without recurrence. Two cases have had further operative procedures for recurrences, but to date are living and well with no recurrences demonstrable.
6. Autopsy findings in two cases of leiomyosarcoma are reported.

We are indebted to the members of the Surgical and Gynecological Staffs of the Methodist Hospital for permission to include their private cases in this series.

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Discussion

DR. J. EDWARD HALL.—I take exception to some of the slides that have been presented here, just as I did when I first saw them.

This is a relatively rare disease, as both speakers mentioned. It has an incidence of 1.4 per cent in the experience of most workers. Kelly and Cullen, in 1,400 fibromyomas, reported an incidence of 1.2 per cent; Maisson, in 4,000 fibromyomas, had an incidence of 1 per cent. The incidence percentage in our own institution, of 1,238 cases, was less than 1 per cent.

I think that it is important to understand percentages when they are given. Dr. Howe, when he started his presentation, stated that sarcomas of the uterus represented 5 per cent of the malignancies of that organ. It must be understood that this is uterine sarcoma and not fibromyoma. Consequently, the figures for both of these conditions are misunderstood. In the Johns Hopkins Hospital, 4 per cent of all uterine malignancies consisted of sarcoma of the uterus.

I wonder whether actually some of the patients who have lived a long time had recurrences of the original tumor, or represented multiplicity of tumor formation. In the case of a patient who after 20 years presents a lesion histologically similar in character to one previously removed, it can very easily be assumed to be from the lesion that was removed originally. At our institution, we recently had a patient who was operated on for multiple myomas of the uterus. Just before closure of the abdomen, as is the custom, the entire peritoneal cavity was explored. A tumor of the small intestine was found which, on histologic examination, proved to be a neurogenic sarcoma. If this lesion had not been found until many years after the pelvic operation, it might have been assumed to have been related to the pelvic tumor. In these instances, two slides, one from the original operation and one from the present operation, are required. A comparison of these slides will show whether the patient has a sarcoma of the uterus at the time of the original surgical procedure and whether the present tumor was a metastasis in the intestine, a frequent situation in such cases.

Involvement of the ileocecal valve in sarcoma of the uterus is a rare condition. Sarcoma of the uterus metastasizes by direct extension through the lymphatics and blood stream, therefore involvement of the liver and lungs is fairly common, but involvement of the ileocecum is unusual.

With respect to the material removed by curettage, again I would question whether it was a myoma of the uterus or diffuse sarcoma of the uterus, possibly from the endometrial tissue itself, from the myometrium, or from the blood vessels of the uterine musculature.

It must be remembered that, embryologically, all uterine tissue arises from the mesoderm; therefore, you may have sarcoma from the myomatous element and also from the epithelial component.

Another point with respect to the anatomy of the myoma is that there is no such thing as a definite capsule of a myoma. Because there is loose areolar tissue separating the myomatous tissue from the surrounding normal uterine musculature, we are apt to think that we separate the myoma from the diffuse normal musculature of the uterus by stripping away the capsule. Histologically, there is no such thing as a capsule as, for example, in the case of a cyst. Therefore, it is easy to understand that if you are dealing with a sarcoma in dissection, especially in a myomectomy, malignant cells may be diffused. That

brings up a very important point, namely, we are apt to be lulled into a false sense of security due to the rarity of the disease, and therefore perform only a supracervical hysterectomy.

I agree with Dr. Davis 100 per cent. Every uterus and every ovarian cyst removed supravaginally should be opened and examined by a competent pathologist at the time of operation to determine the character so that all indicated surgery may be carried out at one operation rather than making it necessary for the patient to return for further surgery.

Dr. FRANK R. SMITH.—Anyone who has listened to this discussion, based on a series of ten cases, will, naturally, ask himself the question: "What possible value can it have?" If you think of the rarity of the condition, you must realize that it takes a long time to collect ten cases of what Dr. Howe chooses to call "unequivocal" sarcoma of the uterus.

I think it was in 1940 that I reported a series of sarcomas of the uterus from Memorial Hospital, covering the period from the time records were made there up to that year. I was able to collect quite a group of so-called sarcomas of the uterus. However, there were only 24 of the so-called "unequivocal" sarcomas. I wish I had known of that term at the time, because to me the term "unequivocal" meant that Doctors James Ewing, Sr., and Fred Stewart agreed that they were real sarcomas. Many patients are sent to us at Memorial Hospital who have had tumors removed elsewhere; slides are sent along with them and these have been classified as sarcomas, whereas, in reality, they are simply cellular myomas.

Another question that occurs to me is the old terminology of malignant degeneration of a fibroid. I have been looking back for such evidence and was successful in finding only one such case; a patient, mentioned by Dr. Frank Foote, of multiple fibroids of the uterus. In that instance the major part of one tumor was composed of simply cellular myoma, and the center looked like a real "unequivocal" sarcoma. That patient, however, did quite well with a simple subtotal hysterectomy.

Of the 24 cases collected, none of the patients lived five years. One patient lived four and one-half years following a supracervical hysterectomy. In cases in which supracervical hysterectomy has been done, however, this not being our usual custom, we have found recurrences in the cervix.

Another thing, I do not think sufficient emphasis has been placed on the matter of x-ray therapy. Constantly we are beset by doctors who have removed uteri, and a diagnosis of sarcoma has been made. I know of no instance of "unequivocal" sarcoma of the uterus where the patient has really derived any benefit from x-ray therapy. X-ray irradiation does not affect leiomyosarcoma of the uterus.

I was interested in hearing Dr. Hall's statement, because we recently have had a patient on whom a hysterectomy for large multiple fibromyoma of the uterus was performed. During the course of the exploration we pulled out a mushroom-like growth which was connected at about the junction of the jejunum and ileum; it looked like a mushroom umbrella and was somewhat softer than the average fibromyoma. Under the microscope it was found to be a leiomyosarcoma with a small base. I did not resect the gut beyond the point of closing it where I resected the growth, and am frank to admit I may not have done enough, although, as I say, the base was very small.

ENDOMETRIOSIS AS A CAUSE OF ILEAL OBSTRUCTION*

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(From the Mayo Foundation and the Mayo Clinic)

THIS paper presents the first analysis of clinical data of a series of cases in which ileal obstruction was caused by endometriosis. The subject is of particular significance because the obstructive involvement of the distal part of the ileum by this highly invasive nonmalignant tissue often has been confused clinically with appendicitis accompanied by ileus, with malignant lesions causing obstruction of the intestine, and with intestinal obstruction caused by the adhesions of pelvic inflammatory disease. The importance of endometriosis as a cause of ileal obstruction has not been sufficiently stressed. The clinical picture of this condition, as revealed by a detailed analysis of the clinical data of sixteen cases, will be presented, as will also (1) certain facts highly pertinent to the differential diagnosis, (2) pathologic lesions and (3) surgical treatment.

The term "endometriosis" indicates the existence of endometrial tissue in any extrauterine location.

Pathogenesis

Counseller classified the theories of the development of endometriosis into three main groups as follows: (1) embryonic pathogenesis, (2) metaplastic pathogenesis, and (3) migratory pathogenesis.

The embryonic theory presupposes a maladjustment on an anatomic basis. The metaplastic theory, in which it is stated that the peritoneum can undergo a change to endometrial tissue, is based on the fact that all genital epithelium and the peritoneum have a common origin from the celomic mesothelium.

The migratory theory assumes that endometriosis has its origin in the uterine mucosa and reaches its extrauterine position by contiguity or invasion, by implantation, and by lymphatic or venous metastasis.

The single theory which best explains all types of endometriosis is that of lymphatic and venous metastasis,^{13, 22} but Sampson's implantation theory plus Harbitz' idea of extraperitonealization seem best to explain endometrioma of the ileum.^{7, 10, 11, 18}

Historical Review of Cases

Mouat, in 1926, reported the first case in which stricture of the ileum was caused by misplaced endometrial tissue on record in the *Quarterly Cumulative Index Medicus*. Starr, in 1929, published a case of endometrioma of the terminal part of the ileum, the appendix, and the cecum, with acute partial intestinal obstruction. The preoperative diagnosis had been acute appendicitis with perforation and partial intestinal obstruction. Of particular interest was the fact that the uterus and adnexa were normal. An unusual aspect of

*Abridgment of a part of a thesis submitted by Dr. McGuff to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery.

the subject was presented when Gale reported an endometrioma of the ileum which had produced intestinal obstruction of sufficient degree to cause impaction of a fish bone and resultant perforation. The bowel exhibited fibrous puckering, with peritoneal adhesions and thickening of the intestinal wall at one point. On microscopie examination, the wall of the bowel was seen to be invaded by endometrial-like tissue.

In 1934, Goodwin⁸ presented a case in which chronic intermittent partial intestinal obstruction of the ileum had been caused by endometriosis. He believed that fibromyoma and uterine retrodisplacement were frequently associated with endometriosis, and that they were possible etiologic factors. Behrendt and Neumeyer² in 1936 reported a case in which chronic partial ileal obstruction had been caused by endometriosis in a single woman, thirty-nine years of age.

Glenn and Thornton⁶ in 1940 published two cases of endometriosis of the ileum with chronic partial intestinal obstruction. They remarked that a review of the English literature for the previous twenty years (1920 to 1940) had revealed only four cases of endometrial implants in the small intestine, with some degree of obstruction present. Grigsby⁹ in 1941 presented two cases in which ileal obstruction had been caused by endometriosis. He noted that the most prominent gross characteristic of endometriosis was the presence of "disintegrating purplish-black blood cysts" on the intestine. Milnor,¹⁴ also in 1941, reported a case of ileal obstruction caused by an endometrioma.

Morrin,¹⁵ in 1942, described a case of complete ileal obstruction caused by endometriosis, and Wood, Diebert, and Kain,²³ in 1946, reported a similar case.

Nature of Present Study

To the time of this report, forty-eight cases are on record in the files of the Mayo Clinic in which the diagnosis of "endometriosis of the bowel" had been made by a pathologist. In three of these cases, pathologic material had been removed during treatment of the clinical symptoms of ileal obstruction caused by endometriosis; an analytic clinicopathologic study of these three cases was made. Thirteen cases of ileal obstruction caused by endometriosis, as reported in the literature, were reviewed. From this, a combined series of sixteen cases of ileal obstruction was assembled.

General Considerations

All patients were white women. The average age of the women was 39.2 years. The oldest was fifty years old and the youngest was thirty-one years old. Ten of the women were in the fourth decade, five were in the fifth decade and only one was in the sixth decade. Eight of the women were married; two were widows; six were single.

Four women complained of absolute sterility, one complained of relative sterility, and two complained of secondary sterility. Among the eight women who had been married and two of the single women, there had been nine pregnancies, with the birth of seven children. In the group of women who had been pregnant, the average period since the last pregnancy was fifteen years. Two of the group previously had undergone pelvic surgical operations.

The average duration of the symptoms of endometriosis was 1.6 years. Five of the patients had complained of acquired dysmenorrhea. The menstrual cycle of eight of the patients was fairly regular, but five patients complained of irregular menstruation. Menorrhagia was a complaint of three women, and metrorrhagia was a complaint of one.

Signs and Symptoms

The average time since the onset of the first symptoms of obstruction of the bowel was 2.3 years. Only two of the patients had lost weight. One had lost 15 pounds (6.8 kg.) and the other, 27 pounds (12.2 kg.). Rectal pain and the passing of grossly bloody stools were not complained of by any patient. Six of the patients complained of comenstrual constipation, seven complained of intermenstrual constipation, and eight complained of either comenstrual or intermenstrual constipation. Diarrhea was a complaint of only one patient.

Consideration of the more direct symptoms of obstruction of the lower part of the small intestine revealed that abdominal pain was the complaint of all sixteen patients. Abdominal distention was the complaint of thirteen patients, and vomiting was a complaint of twelve of the group. Obstipation occurred in five patients. Abdominal tenderness was present in seven patients, and an abdominal mass was palpated in three.

The site of intestinal obstruction in all sixteen of the patients was the distal part of the ileum. Four patients had complete intestinal obstruction, seven had partial intestinal obstruction, and five had chronic intermittent intestinal obstruction.

Diagnosis

A barium enema was administered and roentgenograms of the colon and terminal part of the ileum were made in three cases, and were reported as producing positive results in two, in that the point of obstruction was localized. A plain roentgenogram of the abdomen and a gastro-intestinal roentgenogram were made in two cases. Both demonstrated obstruction of the lower part of the small intestine.

A preoperative diagnosis of endometriosis as the cause of the obstruction was made in three of the sixteen cases. A diagnosis of appendicitis with ileus was made in five cases, of carcinoma of the ileum with obstruction in one case, of carcinoid of the ileum with obstruction in another, and of obstruction of the bowel caused by adhesions from pelvic inflammatory disease in one case. No specific cause of the obstruction was ascertained in the other cases.

Treatment

Ileal resection was uniformly the procedure of choice when endometriosis had caused ileal obstruction. Ileal resection alone was done for seven patients. Enterostomy plus ileal resection were done for one patient. An initial Witzel type of ileostomy and subsequent right hemicolectomy and ileotransverse colostomy were carried out in one patient. Ileal resection plus ileoceceostomy and removal of the remaining tube and ovary were done for one patient. Ileal resection plus panhysterectomy were performed in one case. The short-circuiting operation of ileotransverse colostomy was done for one patient, and panhysterectomy alone was done in one case. In one case, the adhesions of endometriosis were separated to relieve the obstruction.

Results

The condition of all but one of these patients had been followed by examination or by letter for one month to twenty-one years. An excellent result with complete relief of symptoms was obtained for ten patients, a good result with more than fair relief of the symptoms was obtained in three cases, a fair result was secured in one case, and a poor result was reported for two patients (from the literature series) who represented operative

mortalities. These two deaths had occurred before the advent of chemotherapeutic agents, antibiotic agents or anticoagulant preparations. One of the deaths resulted from postoperative peritonitis and the other from pulmonary embolism.

Report of Three Cases

CASE 1.—A single white woman, forty-three years old, complained of lower abdominal cramping pain, abdominal distention, and loud, rumbling sounds in the bowel of two months' duration. She did not have nausea or vomiting. The aforementioned symptoms had been episodic, with increasing frequency. The patient stated that when the cramps became very severe, they suddenly seemed to break through the "stoppage" in the bowel and diarrhea occurred. Blood had not appeared in the stool. The patient had lost 27 pounds (12.2 kg.) in two months.

Physical examination revealed a markedly emaciated, weak, lethargic, white woman who lay with her knees flexed. The abdomen was moderately distended. Peristaltic waves were visible. Abdominal tenderness was absent.

A roentgenogram of the colon was reported as disclosing obstruction of the small intestine. Dilatation of the bowel proximal to the obstruction and a large amount of residual barium were noted.

The patient was treated medically by means of a double lumen tube; 500 c.c. of blood were transfused three times for hypoproteinemia and secondary anemia, and other supportive therapy was carried out in order to get her into the best possible condition for operation, if relief of the obstruction did not develop. The obstruction persisted and became complete one week after admission of the patient.

The patient's abdomen was explored. It was believed that ileocecal obstruction caused by a carcinoid was present. Twenty-eight days after performance of the enterostomy a second operation was done. The distal part of the ileum was found to be dilated to about twice normal size, and was edematous. There was a small mass in the region of the ileocecal juncture, the exact nature of which could not be determined. The right half of the colon, along with the distal foot of ileum, was resected, and side-to-side ileocolostomy was performed. No abnormalities were found in the pelvis and there was no evidence of endometriosis.

The patient made an uneventful recovery. She was released from the hospital on the fourteenth postoperative day. One week later she was dismissed with complete relief of the symptoms of intestinal origin. She weighed 90 pounds (40.8 kg.)—a gain of 15 pounds (6.8 kg.) since her admission.

Pathologic Data.—The specimen consisted of 22 cm. of the terminal part of the ileum, 16 cm. of the cecum (Figs. 1 and 2) and ascending colon, and the appendix. The point of obstruction was 5 cm. proximal to the ileocecal valve. The obstructive process consisted of an extensive blanched area of firm, stenosing endometriosis of the ileum. At the point of obstruction, the ileal mucosa was not involved, but was markedly puckered in a rosette pattern. The ileum proximal to the point of obstruction was markedly dilated to two and a half times normal size, and the wall of the ileum was markedly hypertrophied. Examination of the point of obstruction indicated that the obstruction was complete.

On microscopic examination, the inner portion of the muscularis propria and the submucosa of the ileum were seen to contain diffusely dispersed endometrial glands and stroma in the proliferative phase, and were slightly cystic. A van Gieson stain showed marked fibrosis around one area of endometrial glands and stroma.

Comment on Case.—This case showed how closely a portion of endometriosis of the ileum may mimic a carcinoid with intestinal obstruction in both clinical history and gross appearance.

CASE 2.—A white woman, thirty-three years old, married for nine years but never pregnant, complained of sudden, sharp, severe episodic attacks of pain in the lower and middle parts of the abdomen. She had had such extreme abdominal tenderness at other



Fig. 1.—Distal portion of the ileum and cecum removed in Case 1. An area of endometriosis had caused obstruction 5 cm. proximal to the ileocecal valve. The dilated ileum is above.



Fig. 2.—Section of the ileum removed in Case 1. Note endometrial glands and stroma in the submucosa and in one area just adjacent to the mucosa (hematoxylin and eosin $\times 65$.)

times that she could not walk. The pain had been worse in the few months prior to her admission. She had always been constipated. Acquired dysmenorrhea had become so severe that she would go to bed for the first day of each of her irregular menstrual periods.

On abdominal examination, tenderness in the right lower abdominal quadrant and some rigidity were found. Pelvic examination revealed an irregular, tender mass in the adnexa uteri on the right.

Abdominal exploration was performed; in the lower part of the ileum were found three small contracted and scarred areas. The middle area was the largest. It was producing partial obstruction of the terminal part of the ileum. About 6 inches (15 cm.) of the ileum, including these three areas, were removed, and an end-to-end anastomosis was made. The pathologist reported the condition as multiple endometriomas of the ileum, with partial ileal obstruction.

The patient made an uneventful recovery. She was seen twenty-one years later, at which time relief of symptoms referable to the bowel were complete.

Pathologic Data.—The specimen consisted of 15 cm. of ileum with three endometriomas, each about 6 cm. apart. The ileum proximal to the middle endometrioma was dilated to two and a half times normal size. The mucosa at the site of the endometrioma was puckered, not ulcerated, and was freely movable. The endometriomas were hard; their serosal surfaces had a dimpled and puckered, grayish black, speckled appearance.

Microscopic examination disclosed endometrial glands and stroma in the late differentiative phase in the external longitudinal muscular layer near the serosal side. The van Gieson stain demonstrated moderately increased fibrosis around the islands of endometrial glands and stroma.

CASE 3.—A single white woman, thirty-one years of age, who seven years before had been pregnant, the pregnancy ending in an abortion, complained of intermittent pain in the right lower abdominal quadrant which occurred one week before, during and after menses. The pain had been progressively increasing in severity for nine years. The pain increased in intensity as the period came on, and recently had begun to appear ten days before the onset of menstruation, to continue throughout the period. Recently she had had three attacks of severe pain in the right lower abdominal quadrant. In two of the attacks, maximal intensity of pain was reached immediately after the period. The pain was not related to urination or defecation. For the month prior to the patient's admission, the pain had been situated across the lower part of the abdomen and had been persistent. Heat had afforded no relief.

The patient's menses usually occurred from three to six weeks apart; a scanty flow lasted for six days. Six months previously she had had mild metrorrhagia for six weeks.

Previous surgical procedures were an appendectomy done nine years previously, and three years previously, a left radical mastectomy and right simple mastectomy for bilateral intraductal papillary carcinoma.

On abdominal examination, an unusual, ovoid, flat tumor was palpated in the region of the cecum. This tumor was movable and tender.

Abdominal exploration was performed; right salpingo-oophorectomy and resection of the terminal portion of the ileum, with ileocecostomy and end-to-side anastomosis, were done.

The postoperative diagnosis was endometriosis of the right ovary and terminal part of the ileum, with partial intestinal obstruction.

The patient made an uneventful recovery. Her condition was followed for one and one-half years, at the end of which she was free of symptoms of obstruction but was experiencing marked menometrorrhagia which apparently was due to the progression of the endometriosis.

Pathologic Data.—The specimen consisted of 15 cm. of ileum; 9 cm. from the proximal end there was an area of firm, infiltrating endometriosis, 3 by 2 cm. The intestine proximal to the point of obstruction was dilated to twice normal size, and was moderately

TABLE I

| AGE GROUP | NUMBER | PER CENT |
|-------------|--------|----------|
| 12-20 years | 3 | 1 |
| 21-30 years | 45 | 15 |
| 31-40 years | 103 | 34.3 |
| 41-50 years | 70 | 23.3 |
| 51-60 years | 53 | 17.6 |
| 61-70 years | 22 | 7.3 |
| 71-80 years | 4 | 1.3 |
| Total | 300 | 99.8 |

Analyzing Table I, we find that 151 patients were operated upon before 41 years of age and 149 after 41 years of age, or over one-half of the patients were operated upon in the second 20 years of their lives, while the remaining half of the cases were scattered over the last 40 years of life. In only 56 of these cases were the symptoms less than a year, the shortest period being two weeks and the longest over 24 years, with an average duration of symptoms of 10.5 years before operation.

TABLE II

| CHIEF COMPLAINT | NUMBER | PER CENT |
|--|--------|----------|
| "Falling out" or "bearing down sensation" | 94 | 31.3 |
| Pelvic or low abdominal pain | 64 | 21.3 |
| Backache | 59 | 19.6 |
| Bladder symptoms (frequency, dribbling, stain incontinence) | 57 | 19.0 |
| Vaginal bleeding | 16 | 5.3 |
| Others | 10 | 3.3 |
| Total | 300 | 99.8 |

The great majority of the symptoms are directly referable to the pelvis, easily seen, and many times diagnosed by the patient and yet have been allowed to persist for an average of 10 years before correction. Palliative use of the pessary to confirm the diagnosis will not only give relief but will help to point out coexisting pathology if not relieved.

Orthopedic consultations should be the rule in those cases of persistent backache.

TABLE III

| OTHER ASSOCIATED SYMPTOMS | NUMBER | PER CENT |
|------------------------------|--------|----------|
| Bleeding, abnormal all forms | 119 | 39.6 |
| Leucorrhea | 112 | 37.3 |
| Incontinence | 81 | 27.0 |
| Constipation | 44 | 12.7 |
| Dysmenorrhea | 38 | 12.6 |
| Postmenopausal bleeding | 24 | 8.0 |

The striking finding in this table is the high percentage of cases of vaginal bleeding of all forms. This is the result of, or is associated with, changes in the uterus from congestion, fibroids, or chronic cervical ulceration and is due to some cases, even in the absence of the uterus, to chronic ulcerative vaginitis. The other symptoms are comparatively of little significance.

In the group who had ileal obstruction, the fertility rate was higher; there were fewer associated pelvic lesions, and fewer previous pelvic surgical procedures had been performed. Also, in the group with ileal obstruction, constipation was less frequent; only one patient complained of diarrhea and no patient complained of rectal pain or bloody stools. Vomiting was of much more frequent occurrence than obstipation. Gross blood in the stool usually is not a symptom of endometriosis of the bowel. It was *not* a symptom of ileal involvement in sixteen cases.

When the ileum is obstructed by endometriosis, the prominent symptoms and signs are those of obstruction of the lower part of the small intestine, and, if the correct preoperative diagnosis is to be made, the symptoms of endometriosis generally must be searched for by means of a carefully taken history¹⁷ and thorough abdominal and pelvic examinations. The general symptoms of endometriosis may or may not be present in these patients, but when they are present, the symptoms usually occur to a lesser degree. Most important points in the diagnosis of endometriosis causing ileal obstruction are: (1) sterility of ten to fifteen years' duration, (2) the presence of acquired and increasing dysmenorrhea, (3) menstrual periodicity of the symptoms of endometriosis and moderately progressive ileal obstruction, and (4) the presence of uterine fibroids or ovarian cysts and/or tender nodules in the cul-de-sac of Douglas or along the uterosacral ligaments. The "threshold of suspicion" of the physician should be aroused by the presence of any two of the aforementioned points.⁴

Differential Diagnosis.—Obstruction of the distal part of the ileum by endometriosis often has been thought clinically to be appendicitis accompanied by ileus. As a rule, however, the symptoms of endometriosis are elicited if a thorough history is taken. Definite symptoms of progressive obstruction of the lower part of the small intestine are superimposed upon the periodic menstrual symptoms of increasing acquired dysmenorrhea, abdominal pain, constipation, and so forth. The symptoms of low ileal obstruction are colicky, cramping pain in the lower part of the abdomen or about the umbilicus (usually greater on the right side), abdominal distention, constipation or diarrhea, and fairly early nausea and vomiting. Diarrhea, if present, generally is reflex in origin; if the obstruction persists, the constipation becomes obstipation. The ileal obstruction at first may be moderate in degree, but it progresses rapidly with each menstrual period, to usually acute complete or partial obstruction or to chronic intermittent intestinal obstruction of high or low grade. Ileal obstruction if persistent brings about great physiologic changes,^{1, 21} such as dehydration, loss of chlorides and resultant alkalosis, and loss of plasma.

In five cases (one in the current series and four in the series from the literature), the preoperative diagnosis was appendicitis with ileus. None of the patients concerned had had rectal pain, and only six of the sixteen in the whole series had been constipated. Fewer proportionately (five of sixteen) complained of acquired dysmenorrhea than in a previous general series in which endometriosis also had obstructed the lower bowel; hence, it is easily seen that, in the group of ileal obstruction caused by endometriosis the symptoms of endometriosis are not so striking or prominent as were those in the general series.

The differential diagnosis between ileal obstruction caused by endometriosis and appendicitis²⁰ with ileus may be difficult. However, when a history is carefully taken, the menstrual periodicity of some of the symptoms of endometriosis and of some of the symptoms of a previous episode of "subileus" or mild intestinal obstruction, such as abdominal pain, distention, and nausea

hypertrophied. The mucosa over the site of endometriosis was normal and freely movable. The serosal surface of the area of endometriosis was irregular, puckered, roughened, and speckled grayish black.

Microscopic examination of the section of ileum revealed endometrial glands and stroma in the late differentiative phase diffusely spread through the outer portion of the longitudinal muscular layer, but none were seen in the submucosa. A van Gieson stain demonstrated moderate fibrosis around the endometrial glands and stroma in the outer muscular layer.

Pathologic Considerations

Endometriosis is the only condition of frequent occurrence in women which represents the nonmalignant invasion of other tissues by normal tissue of the same host.¹² Endometriosis, to persist, must have the cyclic hormonal stimulation of the ovaries; in the absence of such stimulation, endometriosis undergoes retrogression. Endometriosis invades the intestinal wall from the serosal side and grows inwardly into the muscularis propria and the submucosa. Rarely has the mucosa of the small intestine been invaded grossly. The intestinal mucosa was intact over the endometriomas in all of the cases studied. In many cases it was adherent or puckered, but it was never ulcerated.

The ileum is not so much obstructed by the pushing-in process of the endometrioma as it is by the effects of a small endometrioma accompanied by superficial adhesions, caused by endometriosis, which kink the intestine.

The tissues studied for this paper were removed surgically from three patients at the clinic. They consisted of two segments of the distal part of the ileum, and one specimen removed by right hemicolectomy. In these three cases in which ileal obstruction occurred and the pathologic material was available for direct study, the cause of obstruction was a combination of (1) an endometrioma impinging into the intestinal lumen, and (2) more superficial areas of endometrial adhesions causing a kinking of the intestine.

Associated pelvic pathologic lesions were present in eight of the patients. Uterine fibroids were found in two of the patients, chocolate cysts of one ovary or both ovaries were present in two patients, and simple ovarian cysts were present in two patients. In two of the patients, pelvic pathologic lesions had been removed at a previous operation.

Histopathologically, the endometrioma of the intestine and the areas of endometriosis consisted of either invasion of the serosa, muscularis propria, and submucosa or any combination of these, by endometrial glands and stroma. The muscularis propria more consistently seemed to contain diffusely dispersed endometrial glands and stroma than did either the serosa or the submucosa. In the ileum, it seemed that the submucosa was only lightly invaded, and the endometrial glands and stroma were dispersed more in the outer muscular layer and in the serosa. Although the endometriomas were not exactly typical of the superficial or diffuse type of endometriosis, they were less deep in situation than are the usual endometriomas of the sigmoid.

Diagnosis.—The first analysis of a series of sixteen cases of ileal obstruction caused by endometriosis has revealed certain important clinical data highly pertinent to the diagnosis of this condition. Comparison of clinical data from this series of cases of ileal obstruction with clinical data in a previously reported series of cases of intestinal obstruction in general caused by endometriosis indicated that ileal obstruction more often occurs in a younger group of women in their upper thirties, who either have no grossly detectable pelvic endometriosis or have much less extensive pelvic endometriosis.

endometriosis and moderately progressive ileal obstruction, and (4) the presence, in half of the cases, of tender nodules in the cul-de-sac of Douglas or along the uterosacral ligaments, or of uterine fibroids or ovarian cysts.

Obstruction of the distal part of the ileum by endometriosis often has been thought clinically to be appendicitis accompanied by ileus. The symptoms of endometriosis generally can be elicited, however, if a thorough history is taken.

The clinical picture of ileal obstruction caused by endometriosis is much less characteristic than that of sigmoidal obstruction.

The treatment of choice in ileal obstruction caused by endometriosis is ileal resection, with or without preliminary ileocolostomy or enterostomy and with or without bilateral oophorectomy and/or hysterectomy, as indicated by the presence and degree of the associated pelvic pathologic processes.

The mechanism of ileal obstruction was found to be due, usually, to kinking caused by the adhesions of endometriosis and, to a lesser degree, to the impingement of the endometrioma into the intestinal lumen. Endometriomas of the ileum were more superficial in location than those of the pelvic part of the colon.

Microscopically, reactive fibrosis around the endometrial glands and stroma was characteristic. Endometrial glands and stroma were found in all layers of the intestinal wall except the mucosa. They were more prominent, however, in the muscularis propria and the serosa.

Histopathologic examination of frozen sections of tissue and pathologic confirmation of endometriosis as the cause of ileal obstruction are imperative in every case, because a malignant process can be excluded only by this procedure.

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or vomiting, usually can be elicited. This is the most important single point in the differential diagnosis between ileal obstruction caused by endometriosis and appendicitis with signs of obstruction.

About half of the patients in this group will be found to have, on pelvic examination, associated pelvic lesions such as tender, endometrial nodules in the cul-de-sac of Douglas, ovarian cysts and, occasionally, uterine fibroids. Hence, the second most important point in the differential diagnosis is the finding of associated pelvic pathologic processes or other signs of pelvic endometriosis.

Third in importance is the characteristically rhythmic chronicity of the manifestations of endometriosis as opposed to a single attack of appendicitis or to, usually, no more than one or two previous nonrhythmic attacks.

Laboratory work in the form of leucocyte counts and differential blood counts does not seem to aid much in the distinction, for in the series leucocyte counts of more than 10,000 per c.mm. often were noted, as were high polymorphonuclear counts. "Point tenderness" seems to be of the utmost importance in the diagnosis of acute appendicitis, as contrasted with the absence of this type of tenderness in ileal obstruction caused by endometriosis. It is easily understood, however, that, at times, the differential diagnosis between these two entities from the standpoint of an emergency clinical preoperative diagnosis might well be impossible.

Treatment.—Surgical treatment is indicated in ileal obstruction caused by endometriosis. The obstruction is caused more by the tough, dense adhesions of endometriosis and the resultant kinking of the intestine than by impingement of the endometrioma into the intestinal lumen. Hence, most of the time, the only way in which the obstruction in the ileum can be overcome, will be resection or a short-circuiting procedure, such as ileotransverse colostomy, which will not remove the lesion. This is true in respect to the ileum, even though it is a basic fact that the retrogression of endometriosis depends upon the absence of ovarian hormonal stimulation, and that bilateral oophorectomy usually produces a certain "relenting" of the lesion.

If there is extensive endometriosis of the pelvic viscera in an older woman, bilateral oophorectomy and hysterectomy also may be done. In a younger woman, with no or only slight pelvic involvement by endometriosis, ileal resection alone should prove sufficient. If the obstruction is complete or of high grade, with great dilatation of the proximal portion of bowel, preliminary enterostomy may be done to relieve the distention, the procedure later to be followed by ileal resection.

Decision to do or not to do bilateral oophorectomy should be based on the location and extent of the endometriosis in the pelvis, the presence and degree of associated pelvic pathologic processes, and the patient's desire for pregnancy and the probability of her becoming pregnant. It might be pointed out that when the pelvic part of the colon is chronically obstructed by endometriosis, bilateral oophorectomy usually is indicated, and that as a rule the bowel should be treated conservatively.

Summary and Conclusions

An analytic study of the clinical data in sixteen cases of ileal obstruction caused by endometriosis has been presented. Three of these cases are from the files of the clinic and thirteen are from the medical literature.

Important points in the diagnosis of endometriosis caused by ileal obstruction are: (1) sterility of more than ten years' duration, (2) increasing acquired dysmenorrhea, (3) menstrual periodicity in the symptoms of

The present cannula (Fig. 1) has developed out of a simple model which we have used since 1946 in 175 cases for cervical obturation. The cannula has the length and diameter of an ordinary uterine sound. It consists of two metal channels, one of which is very narrow and ends about 2 cm. behind the tip of the instrument. Its opening is covered by a thin, elastic rubber tube, 2 to 3 cm. long, which is tied at each end to the shaft of the instrument by surgical silk.*

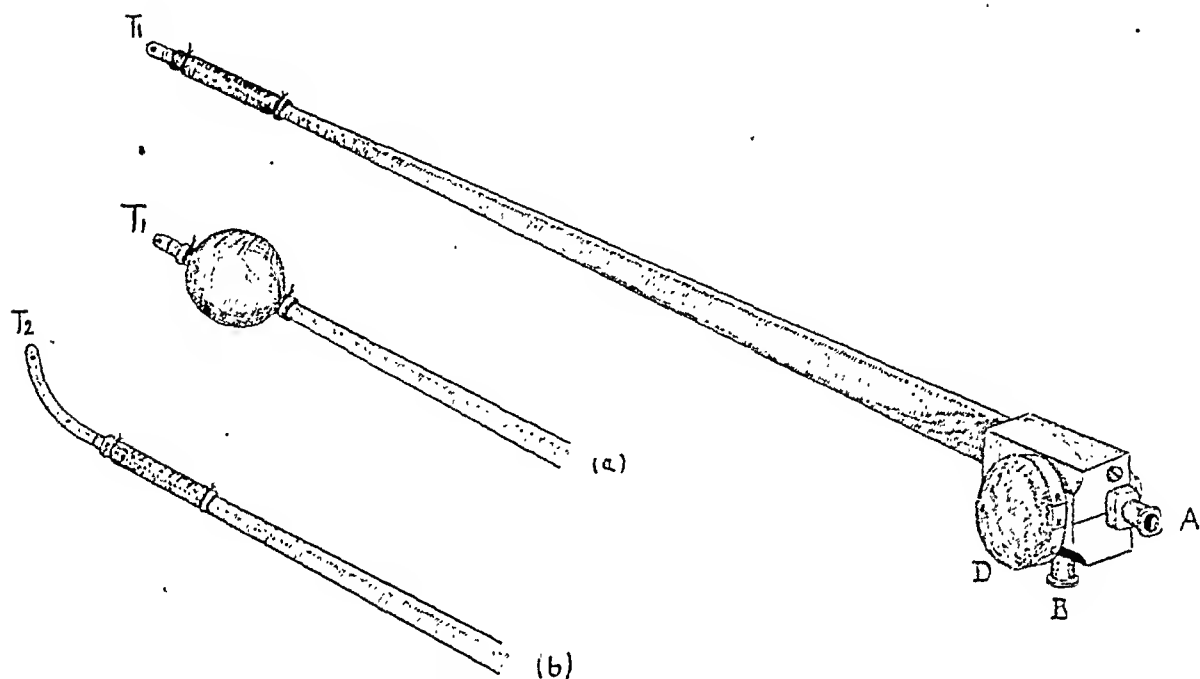


Fig. 1.—Cannula assembled ready for use with revolving disc, hubs for syringe and manometer connections and inflatable tip (letter B below letter C not visible). (a). Rubber tubing distended. (b). Extension tip for insertion into uterine cavity.

The instrument can be inserted easily into any cervical canal which admits a uterine sound. In most cases it is not necessary to grasp the cervix with a tenaculum forceps. The latter can be removed as soon as the rubber-covered tip has been inserted inside the cervical canal. In certain cases, e.g., stenosis of the internal os, it may be desirable to insert the cannula with its tip in the uterine cavity. For such purpose the short tip (T) (Fig. 1) may be replaced by a longer one (T₁) (Fig. 1). Preliminary dilatation, when desirable, should not be done just before the injection of contrast media or before insufflation. So far it has been possible in our cases to introduce the cannula in cervical stenosis after the latter was passed by a uterine sound.

The cannula is inserted with the revolving disc *D* in the position that presents the engraved letter *B* (bulb on the disc) (Fig. 1) opposite a fixed indicator. Through hub *A*, which fits the Luer syringe, 1 to 3 c.c. of water or air are injected and thus the rubber tube at the end of the instrument becomes distended (Fig. 1a). With a little experience one can soon feel whether the bulb is sufficiently expanded. If one is interested in checking the pressure in the inflated balloon, he need only turn the disc to *C*, remove the syringe, and attach a manometer to hub *A*. On turning the disc back to *B*, the pressure within the rubber balloon will be promptly indicated on the manometer. It is to be noted

*The cannula presented here is made and distributed by United Surgical Supply Co., 160 E. 56 Street, New York, N. Y.

CERVICAL OBTURATION WITH INFLATABLE CANNULA IN UTEROTUBAL INSUFFLATION AND HYSTEROSALPINGOGRAPHY

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CERVICAL obturation is of major importance in the technical procedure of uterotubal insufflation and hysteroscopy. Regurgitation of CO₂ gas or oil leads to unreliable estimation of the pressure employed, and not infrequently to wrong interpretation as to tubal patency. Obturation is usually secured by pressing a rubber or metal acorn against the cervical os. This is easily accomplished in the presence of a round and well-shaped external orifice. However, if the external os is irregular in contour as in lacerations and eversion, excessive pressure must be exerted by the acorn in order to prevent leakage of the contrast medium or of CO₂ gas as the case may be. To prevent regurgitation the cervix must be grasped firmly with a tenaculum forceps exerting counter pressure. In this maneuver, the uterus is either pushed upward or drawn down. To keep the balance by equal push and pull is sometimes difficult. The anatomic change in position may occasionally be sufficient to simulate closure of the tubes by causing artificial kinks at the uterotubal junction or by artificially stretching adhesions which do not otherwise obstruct the tubal lumen when the normal position of the uterus is undisturbed. The cannula devised by Colvin with screw tips of various sizes, later modified by Hudgins, affords tight obturation but involves a certain amount of trauma which theoretically may predispose to embolization.

After many years experience with hysterosalpingography and uterotubal insufflation the prerequisites of an ideal uterine cannula appear to be the following:

1. Its application should be painless and unaccompanied by trauma.
2. It must provide airtight obturation of the cervical canal.
3. It should maintain the normal anatomical position of the uterus.

The cannula presented in this paper has been devised with these desiderata in view. It is based on a rather old device, namely, the use of an inflatable rubber bulb in order to change the diameter of a rigid instrument. Nitze, the inventor of the cystoscope, made use of this principle for a ureteral catheter. In 1883, a United States patent was granted to Henry E. Finney for an instrument based on the same principle for "the treatment of the male urethra." About twelve years ago, one of us (I.C.R.) constructed a cannula similar in principle to the one about to be described. Dr. R. B. Stout had the same idea, except that he placed the rubber balloon within the uterine cavity.¹ Decker,² in a recent publication, also recommends inserting the rubber balloon surrounding the cannula tip into the uterine cavity. This principle has been employed by one of us in studying the differential between uterine and tubal contractions during uterotubal insufflation.³

Luer syringe attached to hub A. The disc is turned to position R (= Rubin test) which enables us to measure the exerted pressure by connecting the manometer to hub B. In the simplified test, 20 c.c. of carbon dioxide injected by a syringe is sufficient because of the complete closure of the cervix without any leakage. A sudden fall of manometric pressure is indicative of tubal patency. If shoulder pains result they are minimal.*

By inflating the rubber bulb with an aqueous contrast medium (e.g. diodrast) one can easily demonstrate the relation of the bulb to the cervical canal (Fig. 2). In order to note the distensibility of the intracervical balloon and any changes that the cervical walls might exert upon it, another cannula with the balloon filled with an equal amount of diodrast was exposed at the same time on the same x-ray film. The shape of the balloon inside the cervix may be compared to the external balloon in Fig. 2. In Fig. 3, water has replaced the diodrast and is therefore invisible, while the uterine cavity is seen filled with contrast medium. Incidentally, the cervical balloon reveals a configuration which does not conform to what one notes in conventional drawings of the cervical canal because of distention by the rubber balloon. The cervical canal appears, from our study, to yield readily to a greater degree of dilatation than has hitherto been realized.†

Owing to rigid walls, some cervices were found to resist balloon distention with 2 to 3 c.c. of water. Nevertheless, good obturation could be obtained with less filling. If the rubber part of the instrument is not inserted deep enough into the cervical canal the balloon may bulge through the external os. However, this does not prevent airtight closure. Should the rubber bulb be pushed out entirely from the cervix it may be reinserted and kept in place by grasping the anterior lip of the cervix with a tenaculum forceps. In several cases the cervix was found transformed into a shallow cone. Airtight closure could be obtained in these cases by advancing the expanded rubber bulb into the cone while the cervix was held in place by a tenaculum forceps.

The present cannula has the advantage over the ordinary cannula with an acorn tip in that it brings a larger area of the endocervix in contact with the acorn. Hence, the pressure required to obturate the cervix is less. As this pressure is not only directed upward, but upon all sides, dislocation of the cervix does not as a rule result.

The pressure within the rubber balloon automatically predetermines the maximum pressure which is intended to be used for the insufflation test or salpingography. If, for example in the bulb is 250 mm. Hg and the pressure used during insufflation or salpingography is higher, no matter how little this may be, there is prompt escape of the gas, or oil from the cervix. The same physical law operates here as in measuring blood pressure. If the blood pressure exceeds the pressure in the armcuff, the pulse wave immediately returns. The balloon in the present cannula thus forms a desirable safety valve which automatically prevents an undue increase of pressure inside the uterus.

This feature of the instrument is of importance for salpingography. Usually a contrast medium is used which has a certain viscosity. Pressure determinations when lipiodol or other viscous fluid is used are not accurate because of the considerable friction inside the small lumen of the cannula where a rapid decrease of pressure takes place with each progressive centimeter of the lumen. When the contrast medium enters the uterine cavity the

*The senior author does not recommend or employ the use of the syringe for injecting CO₂ into the uterus for testing tubal patency, preferring insufflation by means of the automatic siphon meter with kymograph. The present cannula is admirably adapted for this apparatus.

†This point of elasticity of the cervix under various conditions will be the basis of a future publication.

that if less than 1 c.c. of air or water is used to inflate the balloon, the pressure readings in the balloon may not be accurate. Now the disc is turned to the position marked by the letter C (closed) and the instrument is ready for the procedure.

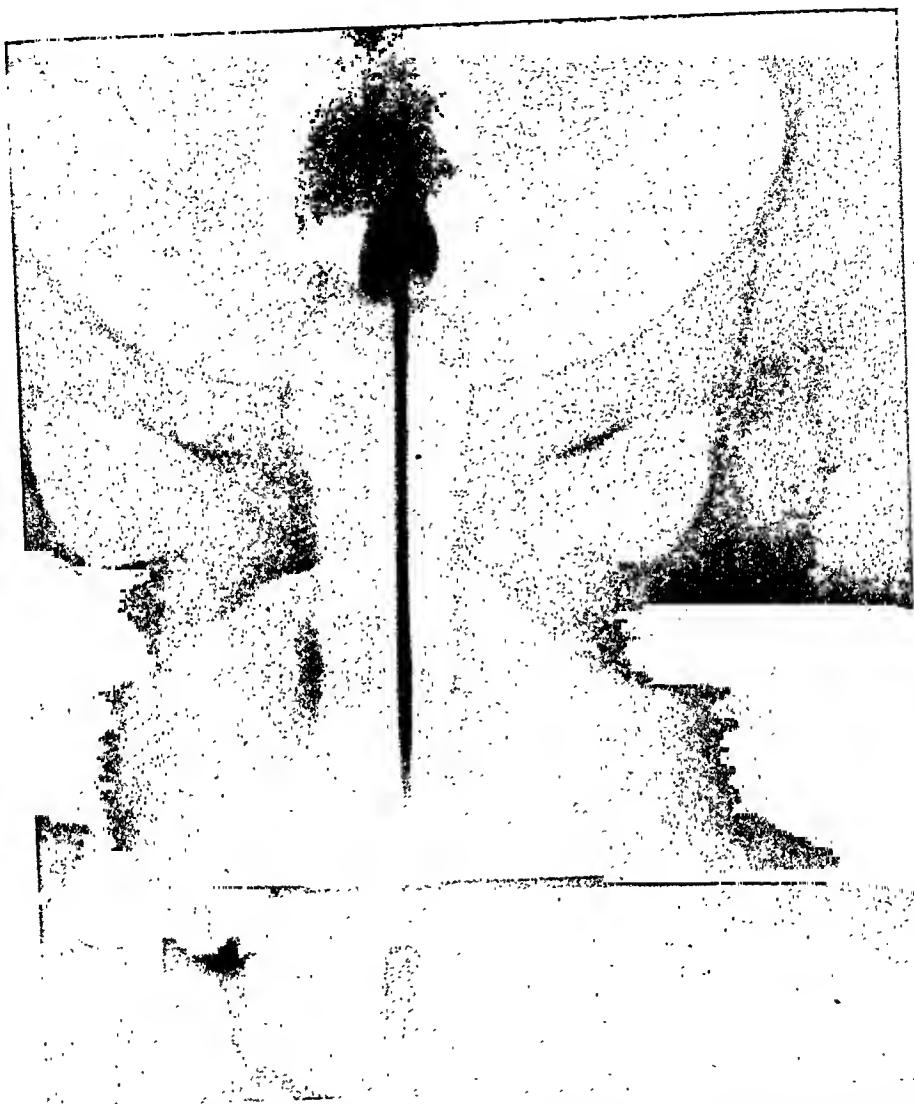


Fig. 2.—Inflatable cannula filled with diodrast obturating the cervical canal. Note that it is pyriform or acorn in shape as compared to the oval-shaped inflated cannula outside of the body.

The disc is now turned to the position X (= x-ray) thus connecting hub A directly with the tip of the instrument inside the cervical canal, or to tip T₂ in the uterine cavity. A Luer syringe containing the contrast medium is connected to hub A and the medium is injected into the uterus and the x-ray exposure follows. For fractional injection of contrast medium, the disc is turned to position C after the first fraction is introduced. Hands and syringe may now be removed because the expanded bulb retains the cannula in situ.* By turning the disc back to position X the second fractional injection can be made, and if need be, a third or fourth.

When the kymograph is employed it is connected to hub A and the disc is turned to position X. The insufflation test can be carried out with a 20 c.c.

*A special clamp adaptable to any vaginal speculum has been devised to keep the cannula in the horizontal position.

Conclusions

The importance of cervical obturation in the procedure of uterotubal insufflation and hysterosalpingography has been emphasized. Desiderata of the ideal uterine cannula are:

1. Painless application unaccompanied by trauma.
2. Airtight closure of the cervical canal.
3. Maintenance of the normal anatomical position of the uterus.

A new cannula with inflatable balloon for cervical obturation has been described.

References

1. Personal communication. Acknowledgment is herewith made to R. B. Stout, M.D., for his kindness in letting us see his instrument.
2. Decker, Albert: AM. J. OBST. & GYNEC. 54: 1077, 1947.
3. Rubin, I. C.: AM. J. OBST. & GYNEC. 45: 419, 1943.

pressure inevitably falls. If tubal obstruction is encountered there is a gradual increase of pressure inside the uterus until it equals that which is exerted by the syringe. Before this point is reached a high pressure may be exerted through the syringe which is not usually appreciated by the operator unless he uses a manometer. The rubber balloon affords safety because when the pressure exceeds that within the bulb, the oil escapes at once through the external cervical os.

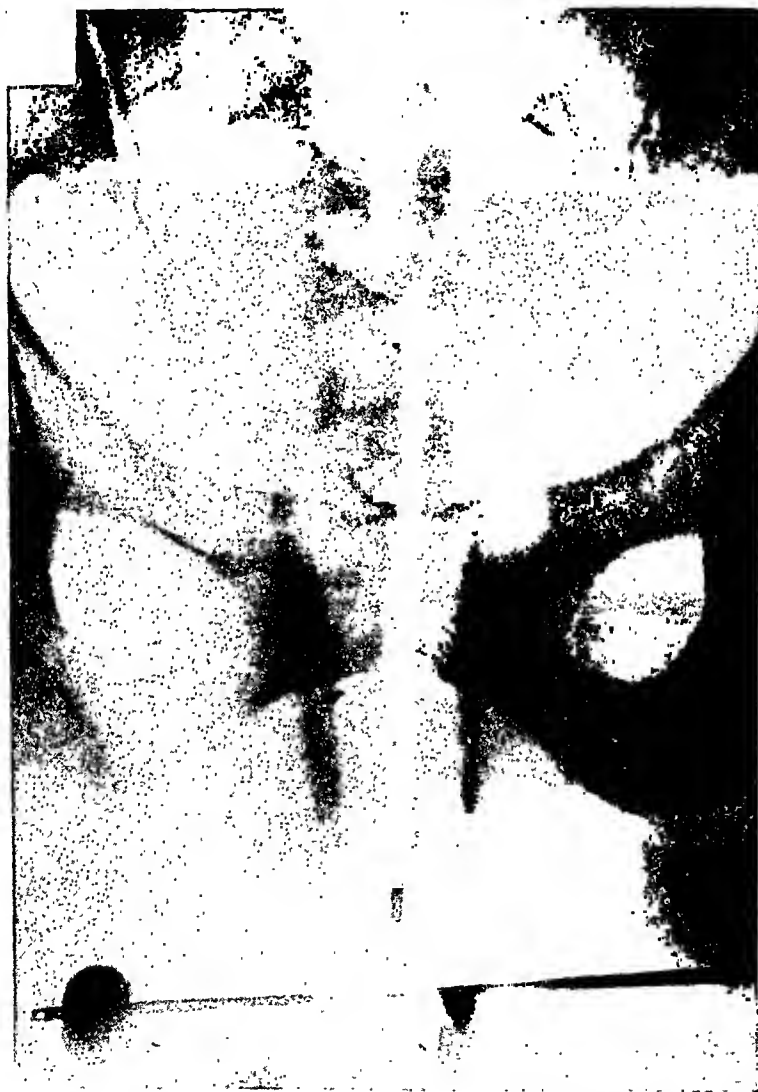


Fig. 3.—Inflatable cannula filled with water (therefore invisible by x-ray) obturating the cervical canal. The contrast medium (rayopaque) demonstrates the uterine cavity. The rubber balloon distended by diodrast is seen below outside of the body for purpose of comparison.

The instrument can be sterilized by boiling. The rubber bulb can stand boiling many times; its cost, however, is so small that it may readily be replaced for each test. We have found it practical to fill the bulb before inserting the cannula in order to note whether it is watertight. However, should the rubber break it is immediately appreciated by the drop in resistance. The water escapes through the external os and does no harm. It is particularly to be noted that the operation of the cannula is exceedingly simple, and after some little experience, requires a minimum of time.

TABLE IV

| COEXISTING MEDICAL COMPLICATIONS | NUMBER | PER CENT |
|----------------------------------|--------|----------|
| Hypertension | 64 | 21.3 |
| Secondary anemia | 28 | 9.3 |
| Syphilis (old) | 10 | 3.0 |
| Early tuberculosis | 6 | 2.0 |
| Diabetes | 3 | 1.0 |
| Total | 111 | |

A total of 111 cases or over one-third of the series had some chronic medical complication coexisting with the pelvic pathology. This tends to increase the risk and lower the chances of satisfactory end results. In addition to the medical complication, associated pathology in the uterus was as follows:

251 instances of chronic cervicitis of varying degrees.

113 had different degrees of uterine prolapse and of these, 48 had had complete prolapse at some time. In no case was carcinoma suspected before operation.

37 cases of uterine fibroids, together with the numerous vascular changes in the uterus, vagina and other pelvic structures.

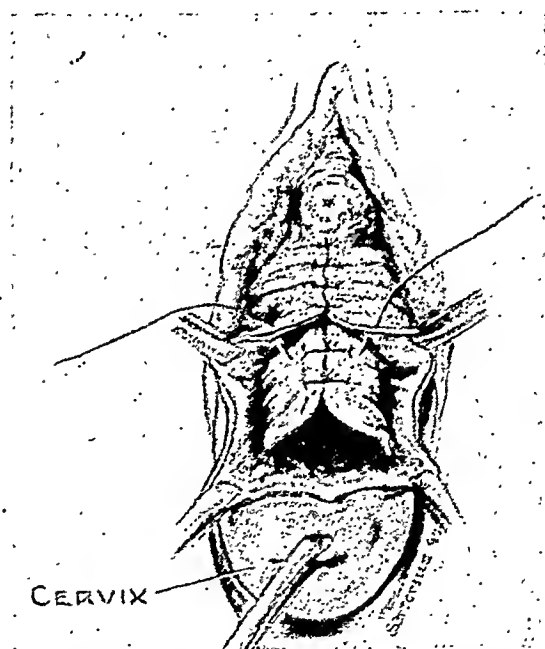


Fig. 3.—Fascia has been completely approximated over urethra and bladder. Excess anterior wall vaginal mucosa excised and edges being approximated. Operation completed.

In every case in this series an anterior and posterior colporrhaphy was done in the following manner: An anatomical dissection and reapproximation of the structures to cure the direct traumatic hernias.

Conditions necessary for the cure of herniation of the pelvic floor:

1. Anatomical repair of pelvic floor that will give sufficient support.
2. Change the vaginal direction so that it goes from the symphysis back to the hollow of the sacrum (in an oblique direction).
3. Lessen the vaginal opening so that the walls will not prolapse through, but vaginal canal must be preserved.

THE DIAGNOSIS OF GENITAL MALIGNANCY BY VAGINAL SMEARS*

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HERE has been a very noticeable increase in life expectancy within recent years. Inflammatory diseases are no longer foremost in the cause of death. Undoubtedly this is the result of improved techniques and better facilities for diagnosis and treatment.

Cancer, on the other hand, now rates second among the causes of death in the United States. Concurrent with this advance in death rate from cancer there has been a remarkable increase in public sentiment toward the disease. Scientific interest and civilian pressure both are activating stimuli to the study of early diagnosis and early treatment of malignancy. Physicians as well as laymen must remember that cancer is curable, but to be cured, it must be diagnosed early.

In 1944, there were 171,171 deaths due to cancer in the United States. Of these, 89,005 occurred in women. Genital cancer was responsible for 22,140 deaths. Because of this preponderance of female genital malignancy, our interest has centered on the vaginal smear as an aid in the early diagnosis of the disease.

Methods

Smears are obtained on all new patients who come to the obstetric and gynecologic clinics, and are requested on all return patients over 30 years of age. Secretions from clinically suspicious genital lesions are obtained for study. It is preferred that a patient does not take a douche on the morning of the expected visit to the clinic. This is not always possible on the first visit, but for subsequent visits it becomes routine.

Two types of smears are made; vaginal and cervical. We believe that neither of the two should be omitted. Frequently, a third type, endocervical or endometrial, is employed according to Papanicolaou and Marchetti.¹

The smears are obtained, stained, and classified according to the works of Papanicolaou² and Papanicolaou and Traut.³ The details of these procedures as we use them have been reported previously by our group.⁴

Results

So far in this study, 6,753 smears on 1,709 patients have been examined. Malignancy was diagnosed by pathology in 124 of these patients. Malignancy was diagnosed by vaginal smears in 114 of these 124 patients, an error of 8.1 per cent. Those missed may be divided into three groups consisting of: (1)

*A part of the expenses incurred in this study was defrayed by funds from a grant to one of us (W.K.C.) by the Research Council of Duke University. The greater part of the expenses, however, was defrayed by funds from a grant to one of us (J.R.K.) by the North Carolina State Laboratory of Hygiene.

†Trainee, National Cancer Institute.

insufficient tissue or poor fixation, three patients; (2) smears obtained after roentgen therapy, three patients; (3) smears missed through not recognizing cancer cells though present, 4 patients.

False positive diagnoses were made in 34 of the remaining 1,585 patients, an error of 2.1 per cent.

TABLE I. SUMMARY OF FALSE POSITIVE SMEAR DIAGNOSES

| | |
|---|----------|
| <i>Patients who had had irradiation for carcinoma</i> | |
| Carcinoma clinically; negative biopsy | 1 |
| Carcinoma clinically; no biopsies | 5 |
| Carcinoma clinically; pathology of biopsy doubtful | 1 |
| No carcinoma clinically; negative biopsies | 6 |
| No carcinoma clinically; no biopsies | 3 |
| | <hr/> 16 |
| <i>Other patients</i> | |
| Those who had negative biopsies | 11 |
| Those who have had no biopsies or follow-ups | 3 |
| Those who had suspicious biopsies; no follow-ups | 4 |
| | <hr/> 18 |
| Total | 34 |

Reports of Patients

The following patients are presented in order that the diagnoses obtained from vaginal smears and biopsies may be compared.

CASE 1.—M. P. The patient, a Negro married woman aged 61 years, para 19-6-7, was seen first in our clinic on May 26, 1947. Her chief complaint was: "Something protruding from my birth canal for seven years." She had had an uneventful menopause eleven years prior. The history elicited four episodes of vaginal spotting during the past eighteen months; the last bleeding was ten days prior to the first visit to the clinic. There was no leucorrhea. The preliminary diagnosis was: postmenopausal bleeding, cause undetermined; chronic cervicitis; prolapsus uteri I-II; cystocele; rectocele. A biopsy made at the time of the first visit was reported as chronic cervicitis. A diagnosis of squamous celled carcinoma of the cervix, type V, was made from vaginal smears obtained at the first visit. The second biopsy obtained on June 3, 1947, was reported as chronic cervicitis. A vaginal hysterectomy, bilateral salpingo-oophorectomy, anterior and posterior colporrhaphy and perineorrhaphy were performed on July 28, 1947. Vaginal smears were diagnosed as type V on this date. The pathology, after numerous serial sections, was reported as early squamous celled carcinoma of the cervix.

CASE 2.—S. McR. The patient, a Negro widowed woman aged 55 years, para 2-1-1, was seen first in the medical clinic for headaches and dizziness on Feb. 5, 1947. She had had an uneventful menopause two years prior. Erosion of the cervix was noted on routine pelvic examination. The preliminary diagnosis was essential hypertension and chronic cervicitis. The report on a biopsy made at the first visit was chronic cervicitis. Vaginal smears were diagnosed as squamous celled carcinoma of the cervix, type IV, at this time. The patient was followed with monthly biopsies and vaginal smears until July 27, 1947, before the smear diagnosis of Feb. 5, 1947 was confirmed by pathology.

CASE 3.—E. W. The patient, a white widowed woman aged 56 years, para 3-0-2, was seen first in our clinic on Nov. 11, 1947, for intermittent postmenopausal bleeding and lower abdominal cramps for one year and five months, respectively. She had had an uneventful menopause six years prior. The pelvic examination revealed a cystocele, a rectocele, and a normal, clean, firm, closed cervix. Speculum examination revealed a clean, well-epithelialized cervix with slight bleeding from the os. Additional bleeding occurred upon sounding the

uterine canal. The preliminary diagnosis was: cystocele, rectocele, and postmenopausal bleeding, cause to be determined. The vaginal smear diagnosis was squamous celled carcinoma, type V, on the first visit. A diagnostic dilatation and curettage and endocervical biopsy were performed on Nov. 13, 1947. The pathologic report was squamous celled carcinoma. Examination of the gross specimen obtained by Wertheim radical hysterectomy and radical pelvic lymphadenectomy revealed a clean negative portio vaginalis. An endophytic neoplasm of the endocervix was found after sagittal section of the uterus and cervix. The regional lymph nodes revealed no metastases.

CASE 4.—O. T. The patient, a white married woman aged 37 years, para 6-0-6, was seen first in our clinic on April 1, 1947, with a referred diagnosis of squamous celled carcinoma of the cervix. She had delivered, spontaneously, a full-term infant three months prior. The last two months of gestation were complicated by pre-eclampsia and intermittent vaginal spotting. There was daily spotting after delivery. Ten days prior to her first visit here, the patient had a diagnostic curettage and cervical biopsy which was reported as squamous celled carcinoma of the cervix. The pathology report on a biopsy obtained on her first visit here was chronic cervicitis without evidence of malignancy. Vaginal smears obtained on April 1, and April 7, 1947, were classified as type V, squamous celled carcinoma of the cervix. The report on a biopsy made on April 8, 1947, confirmed the original diagnosis of squamous celled carcinoma of the cervix made elsewhere. The final pathologic report on the cervix and uterus obtained following radical Wertheim hysterectomy and radical pelvic lymphadenectomy was intraepithelial cervical carcinoma.

CASE 5.—M. N. The patient, a white separated woman aged 55 years, para 7-1-6, was seen first in our clinic on Sept. 15, 1947. She was referred in by her local physician with a diagnosis of a questionable carcinoma of the cervix. She had had an uneventful menopause eight years prior. There had been daily spotting associated with leucorrhea for the past year. The preliminary diagnosis was carcinoma of the cervix, stage I-II. The pathology report on a biopsy obtained on Sept. 15, 1947 was chronic cervicitis with atypicalities of the epithelium. Vaginal smears obtained at this time were classified as squamous celled carcinoma of the cervix, type V. The pathology report on a repeat biopsy obtained Sept. 23, 1947, was epidermoid carcinoma of the cervix, spinal cell type.

CASE 6.—L. S. The patient, a white married woman aged 63 years, para 5-1-4, was admitted to the hospital on July 28, 1947. Her chief complaint was "a growth on the left side of my privates." Menopause followed hysterectomy and partial oophorectomy seventeen years before. There had been a moderate yellowish, watery, vaginal discharge. She had not experienced pruritus. Left inguinal nodes measured approximately 2 by 3 centimeters. They were firm, non-tender and movable. The clinical impression was carcinoma of the vulva with metastases. The pathological report on a biopsy made on July 28, 1947 was squamous celled carcinoma of the vulva. Vaginal smears made on July 29, 1947 were diagnosed type IV, squamous celled carcinoma of the vulva.

CASE 7.—M. H. The patient, a white married woman aged 65 years, para 3-0-0, was seen first in the clinic on Aug. 18, 1947, with postmenopausal spotting of eight months' duration. She had had an uneventful menopause fifteen years before. Six months prior to her first visit here a diagnostic curettage performed elsewhere was reported negative for malignancy. The uterus was found to be small and anterior, but there was thickening in the left adnexal region. A second curettage on Sept. 29, 1947 resulted in negative pathology. The patient was readmitted to the hospital on Nov. 7, 1947 for panhysterectomy because of continued postmenopausal bleeding. Vaginal smears obtained on Nov. 8, 1947 showed adenocarcinoma, type V. Total hysterectomy and bilateral salpingo-oophorectomy were performed on Nov. 9, 1947. The pathologic diagnosis was adenocarcinoma of the left oviduct. The edge of the tumor was reported at 3 cm. distance from the uterine cavity.

CASE 8.—M. C. The patient, a Negro widowed woman aged 78 years, para 3-0-3, was admitted to the hospital on July 9, 1947, because of postmenopausal bleeding. An uneventful

menopause occurred forty years prior. Her blood pressure was 225/120. There was cardiac enlargement. Urine showed 1 plus sugar and 1 plus albumin. Preliminary clinical impression was adenocarcinoma of the endometrium, hypertensive cardiovascular disease, generalized arteriosclerosis, and diabetes mellitus. The pathologic report on tissue removed from the cervical os was acute inflammatory reaction. Vaginal smears made on July 10 and July 15, 1947, were diagnosed type III, suspicious for adenocarcinoma of the endometrium with pyometra. The patient was administered an oral estrogen, 10 mg. twice a day starting on July 15, 1947. Vaginal smears made on July 17, 1947, were diagnosed type IV, adenocarcinoma with atypical malignant cells which did not fully correspond to descriptions of the usual endometrial adenocarcinomatous cells. A total hysterectomy, bilateral salpingo-oophorectomy and appendectomy were performed on July 18, 1947. The operation was done because of continued profuse hemorrhage associated with a soft uterus the size of a four months' pregnancy. The final pathologic report was spindle celled sarcoma of the uterus.

CASE 9.—T. G. The patient, a white married woman aged 61 years, para 2-0-0, was seen first on Nov. 21, 1947, because of postmenopausal spotting for one month. A diagnostic curettage was performed elsewhere on Oct. 27, 1947. The pathologic diagnosis was adenocanthoma of the uterus. Vaginal smears made on Nov. 21, 1947, were diagnosed type II CM, without evidence of malignancy. Repeat smears made on Dec. 9, 1947 were similar; still without evidence of malignancy. A panhysterectomy and bilateral salpingo-oophorectomy were performed on Dec. 10, 1947. Smears were obtained from the endometrial surface of the surgical specimen. Grossly, the lesion appeared most suspicious of malignancy, but the smears showed only hyperplastic endometrial cells. The tissue diagnosis was adenocarcinoma of the endometrium.

CASE 10.—M. S. The patient, a Negro woman aged 23 years, para 4-0-4, was seen in the clinic because of prolonged and excessive bleeding for six weeks. The previous menstrual period was May 15, 1947. The patient's youngest child was 1 year old. There had been no tissue passed per vaginam. The uterus was $1\frac{1}{2}$ times normal size, globoid and soft. Hemoglobin was 49 per cent. A chest plate was negative. Tissue obtained by curettage on June 25, 1947, was suspicious of chorionepithelioma. After complete review of the sections by all members of the Pathology Department, the diagnosis of chorionepithelioma was made. The vaginal smear on July 1, 1947, was type V, with numerous elements of pregnancy-type cells, abortal, but with definite malignant changes. A Wertheim radical hysterectomy and radical lymphadenectomy were performed on July 2, 1947. The pathology report was chorionepithelioma, without evidence of lymph node metastasis. The patient returned on Oct. 9, 1947, with hemoptysis. A chest plate showed pulmonary metastases. Vaginal smears made at this time were diagnosed type I, pregnancy.

Patient 1 came to the clinic with symptoms of prolapsus and gave a history of vaginal spotting. Cancer was diagnosed by smears at the time but was not confirmed by pathology until two months later.

Patient 2 was seen first in the medical clinic because of symptoms of hypertension. Irritation of the cervix was noted on speculum examination. Cancer was diagnosed by smears at this time, but was not confirmed by pathology until five months later.

Patients 1 and 2 illustrate clearly the possibility of detecting early malignancy by smear studies prior to biopsy. Again it must be stressed that this is not an inherent fault of the biopsy method of diagnosis. Cells are shed into the vagina, in intraepithelial carcinoma, although there may be no visual evidence of a cervical lesion. The biopsy method, therefore, is not to be blamed if the biopsy is not taken from the involved area.

Patient 3 came to the clinic with the symptom of postmenopausal bleeding. There were no cervical changes, clinically, in spite of the history. A vaginal smear diagnosis of squamous celled carcinoma was made three days prior to D and C and endocervical biopsy. One sees in this patient the potentialities of the use of smears during the climacteric. Physicians often fail to note the menstrual irregularities which may be due to neoplasm during this

physiologic epoch. The bleeding is attributed so frequently to the climacteric if a clean, negative-appearing cervix is seen. The patient may have an endophytic cancer of the cervix. This may be true also in patients with postmenopausal bleeding, but in our clinic such bleeding is always considered as resulting from a neoplasm until all diagnostic procedures are returned as negative. The patient remains under close scrutiny indefinitely even when the studies are negative.

Patients 4 and 5 had a preliminary diagnosis of cervical carcinoma when seen first in our clinic. Confirmation of the diagnosis was made on the first visit by vaginal smears. The first biopsies obtained here were reported as nonmalignant in each patient. Patient 4, following Wertheim radical hysterectomy and radical pelvic lymphadenectomy, was found to have had an intraepithelial carcinoma. This patient again demonstrates the value of the use of vaginal smears in the diagnosis of genital carcinoma in its preinvasive stage.

The smears on patient 6 show that vulvar epithelium is exfoliated into the vagina, permitting, therefore, diagnosis of vulvar malignancy by this technique.

The smears in patient 7 were strongly positive for adenocarcinoma, although two diagnostic curettages failed to establish a diagnosis of malignancy. This shows that diagnosis of oviduct malignancy is possible by vaginal smears when other procedures fail. This patient did not receive definitive therapy on the basis of smear diagnosis, but was operated upon because of continued undiagnosed postmenopausal bleeding, associated with a thickening which suggested a mass in the left adnexal region.

Patient 8 demonstrates the value of the smear in diagnosing sarcoma of the uterus. The original smear diagnosis of adenocarcinoma was due to the lack of sufficient experience in recognizing sarcomatous cells. Malignancy was identified, though not properly classified. This patient also illustrates the use of estrogens³ to decrease the amount of inflammatory exudate which often masks the epithelial elements in smears.

The smears in patient 9, even when obtained from the tumor surface, failed to show cells which could be called malignant. This instance is reported to show that the smear method of diagnosis is not infallible. Firstly, malignant cells must be present before diagnosis is possible. Secondly, these cells must show the characteristic malignant stigmata. The smears from the tumor surface in this instance contained no malignant appearing cells and furthermore the cells had a less suspicious appearance than did those from other smears which had been confirmed previously as hyperplastic endometrium.

Intrauterine malignancy may be diagnosed by vaginal smears as shown by patient 10.

Discussion

This manner of diagnosing genital malignancy is relatively simple though not inexpensive when one considers the necessary chemicals and technical aid required. The smears are obtained in a short time, but careful and frequently lengthy scrutiny is necessary for interpretation. Thus, if one allots thirty to forty minutes for obtaining, staining, and interpreting the smears, the final smear diagnosis may be completed within a much shorter time than that necessary to obtain a tissue diagnosis.

The interpretation of vaginal smears is difficult but compares favorably to that of bone marrow differentials. The cyclic changes associated with the menses are interpreted with approximately the same degree of difficulty as in reading a white blood cell differential. Characteristics of cells used in making a smear diagnosis of malignancy are quite similar to the individual cellular changes described by pathologists for the diagnosis of intra-epithelial carcinoma.^{5, 6} Pathologists report patients who had tissue changes twelve years prior to the time of invasion.⁶ These changes may be detected in vaginal smears. We feel that this work should be under close supervision of a trained cytologist who is capable of rendering expert interpretation.

The diagnosis of malignancy from smears often may be complicated by malignant appearing cells and nuclei which occur in benign conditions.

Extremely large, hyperchromatic, and malshaped free nuclei may appear in smears of patients having a chronic vaginitis. These nuclei are alarming to the inexperienced. Subtle differences in irregularities and pigmentation of the nuclei rule them out as malignant.

Ayre⁷ has described certain cells which he believes characterize precancerous changes. These cells are seen frequently in our smears but thus far we have not been able to consider them anything but normal. A discussion of Ayre's "precancerous" cells will appear in a paper to be published by our group. These cells previously have caused us much concern and were a complicating factor in making diagnoses.

Intrauterine cells in instances of incomplete abortion may be confusing if cells characteristic of pregnancy, abortion or post partum state are not present. When pregnancy-type cells are present without evidence of abortion the diagnosis is difficult. The intra-uterine cells causing the difficulty resemble very closely malignant squamous cervical cells. In fact, if one were required to make a diagnosis from viewing only a group of these cells, most probably the diagnosis would be squamous celled carcinoma of the cervix. Such smears will be described by us in a subsequent paper.

The most vulnerable point in this particular field is the diagnosis of adenocarcinoma of the endometrium. We agree with other investigators on this point.^{4, 8} It is extremely difficult in many smears to distinguish between the nuclei of hyperplastic endometrial cells and those of a malignant process. This is especially true when large, irregularly shaped, hyperchromatic, free nuclei are present. Under these circumstances, other stigmata of malignancy combined with the experience of the interpreter help to reduce the percentage of error in diagnosis.

Another type of smear which may cause much anxiety to the interpreter is one that shows a pyometra. We know that this often accompanies malignancy of the cervix or corpus uteri. In addition to this clinical knowledge there may be numerous atypical cells which strongly suggest both squamous and adenocarcinoma. When the diagnosis is not clear-cut in such instances, the policy of Papanicolaou is followed. The report is made as doubtful and repeat smears are requested. We agree with Papanicolaou that it is a better practice to be conservative and miss a diagnosis than to brand an innocent one with a malignancy.

Inflammatory processes in general may produce malignant appearing cells. These cells occur often in severe chronic cervicitis, especially when *Trichomonas vaginalis* are present.

Our technique and results are improving in direct ratio to our experience.

This laboratory procedure is rapidly becoming a *must* in the armamentarium of gynecologic studies. The method has important potentialities in screening surveys because of the possibility of earlier detection of cancer than by the biopsy method. We believe that in the future this service can be offered to every physician as are serology examinations at the present time. When this time comes, physicians will be required to do more pelvic examinations when obtaining vaginal smears. The combination of both will result in early detection of malignancies. We will be able then to decrease the death rate in women due to genital cancer.

We wish to emphasize that at the present time we feel that every patient should have pathologic tissue confirmation of smear diagnosis of malignancy before institution of therapy.

Summary

Six thousand, seven hundred fifty-three smears on 1,709 patients have been studied. The smears were obtained, stained, and classified by the methods of Papanicolaou and Traut. One hundred fourteen patients with genital malignancy were diagnosed by smears out of a group of 124 diagnosed by pathology; a percentage error of 8.1.

False positive diagnoses were made in 34 of 1,585 patients; a percentage error of 2.1.

Nine patients have been presented who illustrate the diagnosis of genital carcinoma by the vaginal smear method. These include squamous celled carcinoma of the cervix, 5; squamous celled carcinoma of the vulva, 1; sarcoma of the uterus, 1; and chorionepithelioma, 1. Those patients having squamous celled carcinoma of the cervix show that the diagnosis of malignancy sometimes may be made earlier by smears than by the biopsy method.

Primary adenocarcinoma of the oviduct was revealed in the vaginal smears of one patient.

One patient with adenocarcinoma of the endometrium in which smears were negative even when they were obtained from the tumor surface is reported to show a weakness of the smear method.

Salient features, good and bad, of the vaginal smear method in the diagnosis of genital cancer have been presented.

It is thought that this procedure will become routine in the complete physical examination of women, but that treatment for malignancy should not be instituted prior to pathologic tissue confirmation.

The counter stains used in this study have been made available through the courtesy of Dr. C. E. Folsome of the Ortho Pharmaceutical Corporation, Linden, New Jersey.

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A CRITICAL SURVEY OF THE QUESTIONABLE PELVIS

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WITH the apparent normal implantation of the impregnated ovum, the hazard potential of the gravid state is immediately germinated. Obstetric practice is presuming to acquire more and more the precision of a scientific art. The accuracy of prediction of the mode of delivery is concerned with many factors such as careful anamnesis, with particular emphasis on every phase of previous pregnancies; a complete general physical and endocrinological examination to include special reference to the constitutional habitus; a thorough evaluation of the pelvis in respect to the internal genitals, the fascial supports and the state of the cervix; and, lastly, upon a careful consideration of the bony framework, its special osseous characteristics and essential diameters. The latter, and certainly the most constant factor, presents a real challenge to precision obstetrics in respect to the anticipation of certain mechanisms of labor. It governs one's conduct of a case as regards test of labor, type of forceps used, recourse to internal podalic version and extraction, elective cesarean section, whatever the type, or even the selection of pertinent analgesia or anesthesia. One is constantly striving for the ideal termination of labor, and this paper is intended to present a survey of the factors concerned with such responsibility, and to direct special emphasis to the midplane of the pelvis. For the careful evaluation of this pelvic level one is dependent upon help received from diagnostic roentgen-pelvimetry.

The definition of the normal female pelvis is as elusive as that concerned with any field of medicine, and variations in morphology, however minute, may be innumerable. One is dealing with the mean, rather than the ideal. One's knowledge of the mean diameters is essential to the recognition of the nature of contraction, through the lessening of the essential diameters, of any one plane of the pelvis. The study of measured capacity is that of a fixed factor. One must be cognizant, as well, of others, such as the weight and thickness of the osseous components; any uterine, adnexal, or soft tissue pathology (to include the uterine cervix in the sense of heralding dystocia); the labor pattern and the nature of the expulsive forces; the degree of moldability of the cranial bones in determining the adaptability of the head to the pelvic contours; the flexibility of the pelvis as regards the ligaments and fasciae; and the size and weight of the infant. These latter are, as it were, the insensible factors, and escape the precision that is desirable in the study of the clinical suspect pelvis. One's own observations tend to support the association, as quoted by Kenny,³⁷ of such workers as Caldwell and Moloy, Fishberg and Thoms, of physical characteristics versus pelvic types. These studies are worthy of review.

Of the various attempts at classification of pelves, the Caldwell-Moloy presentation of the gynecoid, android, anthropoid, and platypelloid types appears

to be workable and practicable. The characteristics of these various types, however variable, are now well recognized. No discussion of this sort can be complete without studying most carefully the work of Thoms and his associates.⁵⁵⁻⁶³ In the normal gynecoid pelvis, the anteroposterior, transverse, and posterior sagittal diameters of the inlet are given respectively as 11.5 cm., 13 cm., and 4 cm. The above diameters, as applied to the midplane (the plane passing from the inferior margin of the symphysis pubis through the ischial spines usually to the juncture of the fourth and fifth sacral segments) are 11.5 cm., 10.5 cm. (interspinous) and 5 cm. The biischial (at a level just above the tuberosities) and posterior sagittal diameters of the outlet average 10 cm. and 8.5 cm., respectively.

Although one may acquiesce to the above parent forms, one is impressed with the relatively high incidence of variability; the true incidence, particularly of the mixed types, is thus difficult to ascertain. This difficulty is somewhat obviated by the attitude of Caldwell and co-workers¹¹ of having the first or essential feature refer to the nature of the posterior pelvis, and the lesser-pronounced characteristic governed by that of the anterior segment. They describe five mixed types: the anthropoid-gynecoid, the gynecoid-flat, the android-anthropoid, the android-flat, and the android-gynecoid. It is difficult many times to indicate the variables so simply. This is especially true of the variable relationships between the base characteristics and position of the spines, in the coronal plane (as indicated by the length of the posterior sagittal), and the attitude of the lateral walls. The funnel character, not infrequently seen, may be real or inverted. Thus it may be emphasized that neither the inlet morphology nor the outlet configuration are truly indicative of the spatial features present in the midplane. Herein presents the weakness of clinical mensuration except that one, by careful palpation of every component part of the midpelvic plane, may be suspicious of any of the above-stated departures from the ideal. The roentgenologist is then called upon to indicate the degree of deviation from the normal.

Admitting that much essential information may be gained from a thorough clinical study of the female pelvis, and appreciating at the same time its limitations, one must acknowledge accessory aid from roentgenologic interpretations. One may rightfully state that the midplane is obstetrically a most important pelvic level as regards ultimate fetal salvage. Such study is indicated in:

1. The clinical suspect pelvis, to include all planes.
2. The primigravida with an unengaged head, especially in occiput posterior position, whether or not accompanied by an extension attitude; and especially if attended by a definite overriding with the patient in an extreme lithotomy position.
3. A history of serious dystocia during previous labors, eventuating especially in a mutilated or stillborn fetus.
4. Malpresentation in the elderly primigravida.
5. A history of previous fracture or bony disease of the pelvis. In these instances the inlet, as well, might be suspected.

Granted the fulfillment of the foregoing indications, what have the stereo- and isometric roentgenograms to offer the accoucheur? Knowledge is given as to:

1. The general morphology, to include the mensuration of the essential diameters and the variations of the pelvic shape.
2. The nature and degree of contraction present. In such manner this study may be utilized as well in prognosticating the mechanism of labor.
3. The depth of engagement of the presenting part, as suggested by McLane,⁴⁰ with a note as to the clearance, the character of the sciatic notch, the inclination of the symphysis, the sacral characteristics, the depth of the posterior pelvis, and, in cases of true transverse position, the biparietal diameter of the fetal head.

TABLE

| PELVIC PLANES | 400 CONSECUTIVE CASES (CROSS-SECTION OF REFERRED CASES) AUTHORS | AVERAGE MEAN DIAMETERS OF PATIENTS WITH NORMAL DELIVERIES | |
|----------------------------|--|--|---|
| | | WEINBERG AND SCADRON | SELECTED CASES AUTHORS |
| <i>Inlet:</i> | <i>Sums</i> | <i>Sums</i> | <i>Sums</i> |
| Conjugata vera | 11.40 cm. } 25.10 cm. | 24.80 cm. | 11.77 cm. } 24.89 cm. (11.88 cm.)† (25.44 cm.) |
| Transverse Area (Allen) | 13.70 cm. 122.3 sq. cm. | | 13.12 cm. 121.0 sq. cm. (126.7 sq. cm.) |
| <i>Midplane:</i> | | | |
| Anteroposterior | 11.68 cm. } 21.94 cm. | 15.70 cm. | 11.76 cm. } 22.29 cm. (11.41 cm.) (21.71 cm.) |
| Interspinous | 10.26 cm. } 14.10 cm. | | 10.53 cm. } 14.63 cm. (10.30 cm.) (14.33 cm.) |
| Posterior sagittal | 3.84 cm. | | 4.10 cm. (4.03 cm.) |
| Area (Allen) | 94.4 sq. cm. | | 97.0 sq. cm. (91.7 sq. cm.) |
| <i>Outlet:</i> | | | |
| Anteroposterior | 11.68 cm. | | 11.68 cm. (11.41 cm.) |
| Biischial* (Bituberous) | 8.66 cm. } 16.82 cm. | | 9.42 cm. } 17.40 cm. (11.13 cm.) (18.22 cm.) |
| Posterior sagittal | 8.16 cm. | | 7.98 cm. (7.09 cm.) |

*Our transverse measurement was taken from the bases of the pubic arch and does not represent the wider biischial diameter. Our mean biischial diameter was computed as 11.54 cm.

†The figures in parentheses are those of Ane and Menville, and were derived from a study of 450 cases.

4. Multiplicity and attitudes of the various passengers.
5. Advisability of allowing a test of labor.
6. Viability of the fetus.
7. After the onset of labor, one may note the degree of molding, of lateral flexion, change in station, and the adaptation of the fetal head to the pelvis.

How may one recognize the contracted pelvis? One may think of any deviation from the normal in respect to a lessening of the *mean essential diameters* as an indication of contraction. The incidence and nature of the contracted forms are given in papers by Caldwell and Moloy,⁶⁻¹² Eller and Mengert,¹⁷ Johnson,³²⁻³⁵ Kenny,³⁷ Judson,³⁶ Ane,⁴ Hennessy,²³ and Danforth.¹³

Appreciating the factor of relative degree of pelvic contraction, it might be well to combine such a discussion with that of prognosis of delivery, both before and after the onset of labor. It must be remembered that by the study of the inlet morphology alone, many contracted forms may be overlooked. Moreover, as Steele and Javert have shown,⁵¹⁻⁵⁴ the anteroposterior and transverse diameters are hardly a true index of morphology or volumetric capacity, whether of the pelvic brim or any other plane.

The stereoroentgenopelvimetric study will, however, reveal the true morphology or volumetric capacity of the inlet, with its essential diameters. A determination of the transverse diameters (transverse of the inlet, interspinous, biischial or bituberous, and the base of the pubic arch), the splay of the side walls, the width of Michaelis' rhomboid, and the characteristics of the spines and subpubic angle should be made. The lateral view should include the exact measurements of the conjugate vera; the anteroposterior diameters from the symphysis to both the sacral and coccygeal tips; the depth of the pelvis; the inclination of the pelvic brim; the characteristics of the symphysis and sacrum;

4. Bladder must be properly replaced and supported.
5. Have uterus (if left in) in anterior position with support of cardinal ligament and out of line with axis of vagina.
6. Make repair before the tissues have become so fibrotic that they cannot resume normal function.

In order to correct the associated pathology, in addition to the anterior and posterior colporrhaphies, the following additional operations were done:

TABLE V

| ADDITIONAL OPERATIVE PROCEDURES | NUMBER | PER CENT |
|---|--------|----------|
| Vaginal hysterectomy | 156 | 52.0 |
| Cervical amputations and dilatation and curettage | 65 | 21.6 |
| Abdominal hysterectomy | 26 | 8.6 |
| Dilatation and curettage and cauterization of cervix | 24 | 8.0 |
| Dilatation and curettage with tubal ligation, cervical amputation | 18 | 6.0 |
| 11 patients had previous supravaginal hysterectomy operations | 11 | 3.6 |
| Total | 300 | 99.8 |

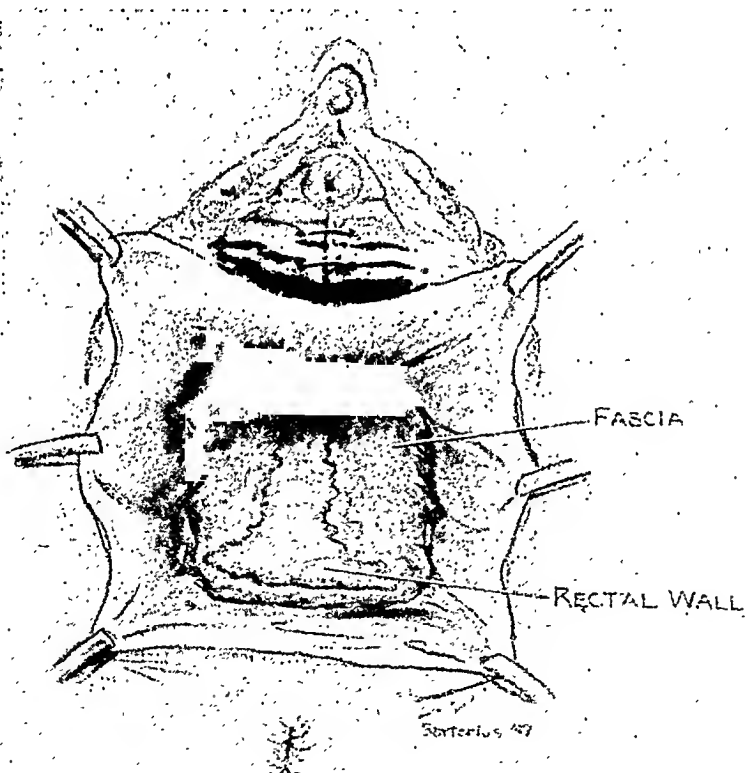


Fig. 4.—Radical repair of rectocele, showing longitudinal splits in the areolar fascia of the posterior vaginal wall.

Time does not permit a discussion of so controversial a combination of operations, but it permits a statement of a few facts: That 11 patients had had previous hysterectomy without any attempt at repair of the cystocele and rectocele. The 18 patients that had amputation of the cervix and tubal ligations were women who had large families beyond their means to care for and conservative measures were instituted rather than have the uterus removed. The

group may be expected to admit the cephalus. A trial of labor is permitted in the contracted pelvis with a c.v. of 8.0 to 10.0 cm., provided that the presenting part can be pushed within 1 cm. of the spines.

It seems fair to state that where one has a combined conjugata vera and transverse inlet sum of less than 23 cm. and/or a combined interspinous and posterior sagittal midplane sum of less than 14 cm., a dystocic labor may be expected. With an inlet sum as low as 23 cm. and a midplane sum of 15 cm. or more, a trial of labor is justified. A test of labor is permissible in an anticipated mild dystocia of the inlet, in the platypelloid (especially with inverted cone characteristics) or other type of pelvis, where the midplane or outlet diameters may be considered adequate. Surgical induction in such questionable cases is attended by too great a risk, and the problem of elective cesarean section in the presence of antepartum rupture of the amnion becomes real. Weinberg and Seadron⁶⁵ have presented an interesting table which may be accepted as workable in respect to inlet pelvimetry as a basis for prognosis. In patients requiring cesarean section, the sum of the interspinous and transverse diameters averaged 23.3 cm. They added that spontaneous deliveries do occur with sums of 22 to 24 cm., and that one may allow a test of labor with values as low as 20 to 22 centimeters. Caldwell and Moloy have postulated that the prognosis of a high head is better if it lay over the posterior segment than if over the anterior. The antithesis is true in the case of the midplane.

In concluding this discussion of the inlet, it might be added that the unengaged head at term, in addition to the suspect pelvis, becomes of significance in respect to the suspect placenta as well as the suspect fetus. In the presence of normal inlet measurements and the inability to force the head into this plane in the extreme lithotomy position, one must exclude the symptomless placenta previa, preferably by a soft-tissue x-ray; also, abnormality of the fetus, inherent or attitudinal; the presence of retroperitoneal solid tumors; and bony disease of the pelvis. The presence of any such adverse factor, especially in the elderly primipara with a posterior or hyperextension attitude, and a long, conical, rigid cervix; or in the multipara with a history of difficult forceps and stillbirth, natural or imposed, should suggest the performance of a cesarean section.

With the head well engaged, either before or after the onset of labor, one's attention is then directed to the midplane, the plane of least pelvic diameters. A midplane contraction should be suspected if any one or more of the following conditions accrue:

1. A constitutionally male type of patient.
2. A diagnosis of an android pelvis or android modification of other pelvic forms clinically, and supported by roentgen morphologic study. It is interesting to note that in difficult labors the incidence of android characters is a third greater than in an unselected group.
3. Prominent and close spines, as determined by palpation.
4. Contracted outlet in the presence of a narrowed forepelvis and subpubic angle, and a flat sacrum. It is commonly appreciated that transverse contraction of the midplane is often associated with a narrow, angulated, and obstetrically useless forepelvis.
5. Premature rupture of membranes.
6. Malposition, especially as refers to transverse and posterior arrests, with or without full dilatation. Figures for this plane in the normal, borderline and absolute contracted forms have been presented in the foregoing table.

The interspinous diameter is most important but an attending compensatory space may be influenced by the splay of the side walls; the antero-posterior and posterior sagittal diameters; and by the characteristics of the sacrum and the sacrosciatic notch. McSweeney and Moloney⁴¹ found the interspinous diameter greater than 9.0 cm. in 84 per cent, 9.0 cm. or less in

I

| HODGES AND DIPPEL SUSPECT PELVES | GRABER AND KANTER | |
|---|--|--|
| | BORDERLINE CONTRACTIONS | ABSOLUTE CONTRACTIONS |
| <i>Sums</i> | <i>Sums</i> | <i>Sums</i> |
| 10.50 cm. } 13.50 cm. } 24.00 cm. 111.0 sq. cm. | 8.0-9.5 cm. | 8.0-8.5 cm. |
| 11.5-12.0 cm. } 10.5 cm. } 22.0-22.5 cm. 4.0 cm. } 14.50 cm. 94.5-98.7 sq. cm. | 8.0-9.5 cm. } 4.0-3.5 cm. } 12.5-13.5 cm. | 8.0 cm. } 3.0-3.5 cm. } 11.0-11.5 cm. |
| 11.5-12.0 cm. 10.00 cm. } 6.0-7.0 cm } 16.0-17.0 cm. | 8.5-9.0 cm. } 6.0 cm. } 14.5-15.0 cm. | 8.0 cm. } 5.0 cm. } 13.0 cm. |

the amount of free space between the fetal head and inlet; the nature of the sacrospinous notch; and, in the case of the true lateral view of the fetal head, its biparietal diameter.

Our experience is in agreement with the stated fact that actual contraction is less frequent than diagnosed clinically. Granted that the morphologic features of all pelvises are essential to the understanding of volumetric capacity, a definite practical application of vital diameters is acceptable. It is particularly applicable in aiding more accurately to visualize that most important part of the obstetric pelvis, the posterior segment, and its counterpart, compensatory space. To illustrate certain salient features of the suspect pelvis, the following table presents a summary of inlet, midplane, and outlet measurements, as seen in the normal, borderline, and contracted pelvis.

Table I would seem to indicate that major thought was directed to the midplane in that the sums of the essential diameters and the area values of the inlet, in our cross-section of referred cases of, respectively, 25.10 cm. and 122.3 sq. cm., agree favorably with those of 24.89 cm. and 121.5 sq. cm. in the spontaneous deliveries. The sums of the anteroposterior and the interspinous diameters of the former agree most closely to those of the suspect pelvises of our selected cases, and to those of Hodges and Dipple.

The precision evidence that is made possible by present methods of roentgenpelvimetry should permit some ease and certainty of prognosis of labor. Granted that a comprehensive impression of the pelvis is important, the study should be further broken down in the manner of individualizing each plane. Even then, errors of prognosis are possible. Williams⁶⁷ has stated that difficulty is often anticipated where none is encountered; and, conversely, dystocia is rarely experienced when none is prognosticated. Jacobs,^{28, 29} Ane and Menville, Klingensmith and Barden²⁸ entertain an interesting discussion as to prognosis. Only the android forms with a conjugata vera as little as 10.00 cm. are associated with a high incidence of cesarean section. A conjugata vera of 11.00 cm. in this

15 per cent, and less than 8.0 cm. in 1 per cent of cases. They anticipate dystocia where the posterior sagittal is less than 3.5 cm. In Ane and Menville's series, 52 of 61 cases with a contraction of 10 mm. or more, in one or more diameters, required an operative delivery.⁴ Of 44 patients where the interspinous or bischial diameters were reduced 10 mm. or more, only 3 to 7 per cent delivered normally. Guerriero and associates²² anticipate dystocia where the conjugata vera is less than 9 cm. and the sum of the interspinous and posterior sagittal diameters is less than 13.5 centimeters. Weinberg and Seadron⁶⁷ place the latter value at 13.0 cm. Our figures tend to support the latter authors. Weinberg and Seadron also state that midforceps extractions are common with a summary measurement directed toward 14.0 cm. from the normal; that delivery from below is rarely accomplished with a value of 13.5 cm. or less; and almost never when the figure becomes 13.0 or less. As may be noted below, our experience has not proved to be quite as severe as this. The discrepancy may be explained by the fact that our sacral end point almost always falls nearer the junction of the fourth and fifth sacral segment, rather than at the tip of the sacrum. A midplane sum of 14.9 was common to their midforceps and one of 13.0 to the section cases.

A different approach to this problem by our English confreres is worthy of note. Williams and Phillips⁶⁷ employ lateral and frontal projection charts, a method that permits them a most favorable prognosis percentage. Nicholson and Allen,⁴⁵ working with the square root of the product of two essential diameters, arrived at a workable formula for determining the area of each pelvic plane in square centimeters. Allen,^{1, 2} whose table of prognosis is most workable, may be commended for his application of this scheme. A conjugate of 10.3 cm. or less portends an abnormal labor, and a normal labor is assured with one of 13.7 cm. or greater. The critical level for the conjugate is given as 11.4 cm., and that of the transverse is 12.3 cm. If either the conjugate or the brim area is reduced to 105 sq. cm. or lower, one should consider the possibility of delivery by cesarean section. Such a termination becomes a decided probability if reduced to 90 sq. cm. A normal delivery is assured with a value of 130 sq. cm. or more.

In his study of the midplane, Allen gives the critical levels of 11.3 cm. and 9.5 cm. for the anteroposterior and interspinous diameters, respectively. Our experience is in agreement with his statement that if the interspinous is the critical diameter, one would expect more arrests with the above critical level than we have encountered. He, therefore, makes use of a transverse diameter taken between the flat opposing surfaces of the ischia anterior to the bases of the spinous processes. This diameter's critical level is 10.9 cm. This becomes important as an index of anterior compensatory space if the interspinous is less than 10 centimeters. The critical area level is 90 sq. cm., using the interspinous diameter, and 104 employing the transverse. Ince and Young²⁷ feel that normal delivery is possible at an 85 sq. cm. level. Williams and Phillips⁶⁷ suggest that the prognosis is serious if the anteroposterior and interspinous are less than 10.1 cm. and 9.6 cm., respectively. Allen, concurring with the above, states that a vaginal delivery becomes uncertain with an area value of 85 square centimeters. Using the bispinous diameter instead of the transverse, this figure becomes 10 to 15 sq. cm. less, or 70 to 75 square centimeters. He maintains that a normal delivery is almost certain with an area of 110 sq. cm. and an interspinous of 10 centimeters. Allen's article presents a workable table of prognosis in concentrating on area values for the various planes of importance.

In the last of the pelvic planes to merit discussion, the outlet, interest is directed mainly to the angle and nature of the pubic arch; the characteristics of the fascial pelvic floor; the thickness of the perineal body; and the pubo-sacral, pubococcygeal, bischial, and posterior sagittal diameters. Williams and

TABLE III. EFFECT OF INLET CONTRACTIONS

| INLET DIAMETERS (IN CMS.) | C. FORCEPS DELIVERIES | | | | D. SPONTANEOUS DELIVERIES† |
|--|---|--|---|--|--|
| | A. ELECTIVE CESAREAN SECTION** | B. INTRAPARTUM CESAREAN SECTION† | HIGH FORCEPS‡ | MIDFORCEPS§ | LOW FORCEPS |
| I. Conjugate vera under 10: Conjugate vera Transverse Area (in sq. cm.) | (7 cases) 9.39 } 22.18 12.79 } 94.2 | (5 cases) 10.80 } 22.40 11.60 } 98.1 | (2 cases) 9.30 } 21.55 12.25 } 89.6 | (1 case) 9.60 } 23.20 13.60 } 102.0 | (1 case) 9.0 } 20.90 11.9 } 84.6 (Stillborn) |
| II. Conjugate vera 10-10.5: Conjugate vera Transverse Area | (10 cases) 10.25 } 22.72 12.47 } 110.8 | (3 cases) 10.27 } 22.55 12.28 } 99.2 | (2 cases) 10.20 } 22.90 12.70 } 101.0 (Axis traction) | | (3 cases) 10.30 } 23.76 13.46 } 108.8 (1 breech extraction) |
| III. Conjugate vera 10.5-11: Conjugate vera Transverse Area Midplane sum | (7 cases) 10.67 } 23.90 13.23 } 110.6 | (3 cases)†† 10.70 } 23.40 12.70 } 106.4 | | (5 cases)‡‡ 10.72 } 23.09 12.37 } 103.9 12.57 (20.90)§§ (1 axis traction) | (2 cases) 10.75 } 24.40 13.65 } 104.8 16.35 (22.80) |
| IV. Conjugate vera over 11, but a combined e.v. and tr. under 24 Conjugate vera Transverse Area Midplane sum | (10 cases)** 11.43 } 23.57 12.14 } 108.9 | | | (3 cases) 11.33 } 23.46 12.13 } 107.1 13.77 (21.70) (2 axis traction) | (5 cases) 11.90 } 23.20 11.30 } 105.3 13.7 (21.50) |
| V. Conjugate vera over 11, but a combined e.v. and tr. over 24 Conjugate vera Transverse Area Midplane sum | | | | | (5 cases) 12.22 } 26.30 14.08 } 134.7 16.10 (22.58) |

*The mean average weight of babies in this group (A) were: I, 3,376 Gm.; II, 3,300 Gm.; III, 3,370 Gm.; and IV, 3,307 Gm.
†Mean average baby weight and mean average hours of labor were (B): I, 3,737 Gm., 12 hrs.; II, 3,538 Gm., 5 hrs.; III, 3,606 Gm., and 41 hrs.

‡Weight and hours here were (C): I, 3,375 Gm., 17 hrs.; II, 3,368 Gm., 13.5 hrs.

§Weight and hours here were (C): I, 3,280 Gm., 13 hrs.; III, 3,485 Gm., 45 hrs.; IV, 3,401 Gm., 24 hrs.

||Weight and hours here were (C): I, 2,990 Gm., 14 hrs.; III, 3,410 Gm., 39 hrs.

¶Weight and hours of this group were (D): II, 3,085 Gm., 15.3 hrs.; III, 3,585 Gm., 14.5 hrs.; IV, 2,435 Gm., 14 hrs.; and V, 3,587 Gm., 12 hrs.

**Included here (A) were 1 breech, 6 midplane contractions, and 1 previous cesarean section.

††Included (B) 1 brow presentation, Wt. 4,048 Gm.

#There was one case with prolapsed cord; normal sums are not included. Those with normal midplane sums are not included in this group (C).

§§The figures in parentheses represent sums of anteroposterior and intersphous, as compared with the midplane sum of the intersphous and posterior sagittal diameter.

Phillips⁶⁷ stressed the anteroposterior and interspinous diameters of the outlet. The former may be as little as 9.5 cm., and the latter 9.14 cm. without resulting in an arrest. An interspinous of less than 9.64 cm. associated with an anteroposterior of less than 10.15 cm., along with a narrow arch, may prove serious. The discussions in this vein, of Ragan,⁴⁷ Williams,⁶⁶ Walsh,⁶⁴ and Eller and Mengert^{17, 18} are worthy of review.

From a diligent study of the influential accessible factors as described above, one may attempt, in the individual case, to prognosticate the mechanism of labor to follow. The inaccessible factors come into play with the onset of labor. With experience, the size of the baby may be estimated with some degree of practicability. In the contracted pelvis, with a minor reduction in any of the mean diameters of any one plane, a baby of less than 3,200 to 3,300 Gm., with average forceful pains and moldability of the head, with or without the aid of forceps, should deliver. In the case of cephalopelvic disproportion at the inlet, with progressive limitation of space in successive planes, a test of labor is unwarranted.

For the sake of brevity, the study of mechanism of labor as presented by Barnes, Caldwell and co-workers, has reluctantly been excluded from this discussion. Suffice it to say, where an arrest is encountered, in the android, android-gynecoid, and android-anthropoid pelvis, rotation in the plane of arrest should be attempted, but not forced. One may have to resort to traction with low rotation, high manual rotation with subsequent forceps extraction, or internal podalic version with breech extraction. In the case of transverse arrest, especially in the platypelloid pelvis, the head may have to be brought down, with or without lateral flexion, and rotated under the pubic arch. If the converging sidewalls are crowded by narrow spines, rotation to an oblique position should be effected before traction is applied. Once the cephalus has reached the bony outlet, delivery may be completed without difficulty.

The tables to follow are intended to reveal the mean diameters and area levels found in the conditions alluded to therein. Table II represents a cross section of cases in general.

From the study of this table, one will note that no difficulties were encountered with the values revealed in column one. Although open to some question, operative deliveries were performed in the presence of apparently normal measurements, as represented in column two. It is in this group that the incidence of cesarean section can be reduced. The sections, as shown in column three, are justified. Midplane arrests may be anticipated with babies weighing 3,563 Gm., with the summary values of the midplane of 21.4 cm. and 13.44 cm. for the anteroposterior and interspinous diameters, respectively, and 89 sq. cm. for the area value. Column six suggests that these labors may be allowed to progress in anticipation of merely performing a delivery by outlet forceps. Column five offers some assurance that a spontaneous outcome is possible for a baby weighing 3,125 Gm., with midplane summary values of 20.67 cm. and 12.81 cm., and an area of 82.6 square centimeters.

Table III concerns the inlet, and the cases represented therein are broken down according to the degree of contraction present.

In the foregoing table, four patients of Group II-A with a combined average mean of 24.37 cm. had a complicating toxemia. They might have been allowed a test of labor. Cesarean section was done in two cases of Group II-B after six hours of no progress, with membranes ruptured.

In studying Table III, the following features are noted:

1. All deliveries were understandably operative in Groups I-A and I-B.
2. Decision as to elective section may be questioned in Groups II-A, III-A, and eight of the cases included in IV-A.
3. The intrapartum cesarean sections require no explanation.

TABLE IV. EFFECT OF MIDPLANE CONTRACTIONS

| MIDPLANES IN DIAMETERS (IN CMS.) | A. ELECTIVE CESAREAN SECTION* | B. INTRAPARTUM CESAREAN SECTION† | C. FORCEPS DELIVERIES‡ | D. SPONTANEOUS DELIVERIES§ |
|--|---|---|--|--|
| | (27 cases) Sums | (2 cases) Sums | (17 cases)¶ Sums | (3 cases) Sums |
| I. Interspinous plus posterior sagittal under 13.0: | | | | |
| Anteroposterior | 11.07 | 11.20 | 11.07 | 11.53 |
| Interspinous | 9.09 | 9.85 | 9.29 | 9.30 |
| Posterior sagittal | 3.03 | 2.85 | 3.05 | 3.27 |
| Area (in sq. cm.) | 79.1 | 68.2 | 80.8 | 83.8 |
| II. I.S. plus P.S. 13.1-13.6: | (1 previous cesarean section) | (1 case) 11.10 9.8 3.3 84.4 | (8 cases)¶ 11.20 9.77 3.76 85.9 | (1 case) 10.50 10.30 2.85 88.7 (Extreme molding of head) |
| Anteroposterior | | | | |
| Interspinous | | 20.90 | 20.97 | 20.80 |
| Posterior sagittal | | 13.10 | 13.53 | 13.15 |
| Area | | | | |
| III. I.S. plus P.S. 13.6-14.1: | (4 cases) 11.50 10.28 3.38 94.7 | | (4 cases)** 11.25 10.25 3.55 91.1 | (3 cases) 12.90 9.75 4.0 97.0 |
| Anteroposterior | | | | |
| Interspinous | 21.78 | | 21.50 | 22.65 |
| Posterior sagittal | 13.66 | | 13.77 | 13.75 |
| Area | | | | |
| IV. I.S. plus P.S. 14.1-14.6: | (2 cases) 11.40 10.00 4.10 88.3 | | (5 cases)†† 12.85 10.12 4.18 102.0 | (3 cases) 11.45 10.00 4.20 90.0 (All breech presentations) |
| Anteroposterior | | | | |
| Interspinous | 21.40 | | 22.97 | 21.45 |
| Posterior sagittal | 14.10 | | 14.30 | 14.20 |
| Area | | | | |
| V. I.S. plus P.S. over 14.6: | | | (6 cases)‡‡ 12.81 10.73 4.90 107.2 | (2 cases) 11.92 11.15 3.65 108.0 |
| Anteroposterior | | | | |
| Interspinous | | | 23.54 | 23.07 |
| Posterior sagittal | | | 15.63 | 14.80 |
| Area | | | | |

*The mean average weight of babies in this group (A) were: I, 3,375 Gm.; III, 3,495 Gm.; IV, 3,390 Gm.

†Mean average baby weight and mean average hours of labor (B) were: I, 3,964 Gm., 5 hours; II, 4,048 Gm., 5 hrs.

‡Weight and hours here (C) were: I, 3,514 Gm., 27 hrs.; II, 3,585 Gm., 18.3 hrs.; III, 3,616 Gm., 38.2 hrs.; IV, 3,156 Gm., 26.5 hrs.; and V, 3,687 Gm., 18 hrs.

§Weight and hours here (D) were: I, 3,173 Gm., 19 hrs.; II, 3,480 Gm., 14 hrs.; III, 3,590 Gm., 16 hrs.; IV, 3,572 Gm., 26 hrs.; and V, 3,350 Gm., 18.5 hrs.

¶In this group (C), 8 were axis traction, 4 midforceps, 4 essential low forceps, and 1 breech.

‡These (C) included 3 axis traction, 2 midforceps, and 2 essential low forceps.

**Here, (C), 2 were midforceps, and 2 were essential low forceps.

††Among these, (C), 2 were axis tractions, 2 midforceps, and 1 high midforceps.

#These (C) represented 4 midforceps, (3 being posteriors), and two essential low forceps.

4. The relatively high incidence of forceps deliveries in Groups II-C, III-C, and IV-C are accounted for, in some instances, by an accompanying midplane crowding, as an expression of android and small gynecoid characters. These modifications, which did not apply to the spontaneous deliveries, are revealed in the numbers in parentheses. These numbers represent the sums of the anteroposterior and transverse diameters of the midplane.

5. Added deductions are included in the discussion of the paper.

Table IV represents an analysis of midplane contractions according to degree, and the types of deliveries that eventuated.

Discussion

A review of the literature and a careful analysis of our own work in the study of the suspect pelvis would seem to indicate that, although great strides have been made toward the proper conduct of labor, even greater success is possible. The roentgenologist is in the position to offer us reasonably accurate and dependable precision data. This may still be regarded as an accessory aid, and is secondary to one's obstetric judgment. A meticulous study of each individual plane is mandatory.

The incidence of contracted forms has been given as 8.3 to 25.1 per cent; the greater number conforming to the platypelloid, small gynecoid, and the android types; and the least to the anthropoid configuration. In this series of cases, the end points being similar to those of Hodges and Dipple, the mean true conjugate vera was 11.4 cm., the transverse 13.7 cm., and the sum of the two was 25.1 centimeters. For the spontaneous deliveries, these values were respectively 11.77 cm., 13.2 cm., and 24.89 centimeters. The corresponding values for the contracted pelvis were found to be significantly lower, and are represented in Tables III and IV. The pelvic inlet plane area for the spontaneous group is given as 121.96 square centimeters. The critical level appears to be 115 square centimeters. Vaginal delivery is uncertain where the value is less than 90 square centimeters, and the possibility of cesarean section must be considered when this figure approaches 105 square centimeters (Allen).

In respect to the midplane in this "suspect" classification, the values for the anteroposterior, the interspinous, and the posterior sagittal are, respectively, 11.76 cm., 10.53 cm., and 4.10 centimeters. The sum of the former two is 21.94 cm., and of the latter two, 14.62 centimeters. The plane area is 98.20 square centimeters. The critical level for the transverse of Allen is 10.9 centimeters. Allen, using his transverse component, places the critical level at 104 sq. cm., or 90 sq. cm., using the interspinous diameter. According to him, vaginal delivery becomes uncertain at a value of 85 sq. cm. (70 to 75 sq. cm. employing the interspinous diameter), and the prognosis is serious if the figure is 76 sq. cm. or less. Vaginal delivery is almost certain when the area proximates 110 sq. cm., and the interspinous is 10 centimeters. To this, our experience seems to agree.

As regards the outlet, the average pubic bituberous (the end points located at the base of the pubic arch) is 8.66 cm.; and the posterior sagittal is 8.16 cm., thus giving a sum of 16.82 centimeters. Allen found that a posterior sagittal of 4.8 cm. or less offered a poor prognosis. A value of 6.5 cm. would suggest a normal delivery.

Since this series represents cases in which the referring clinician suspected some degree of cephalopelvic disproportion, the values may be considered a mildly critical level for the plane concerned, at or above which a spontaneous delivery may be anticipated.

Our findings for the inlet plane (Table III) support the implications as set forth in the table of Weinberg and Scadron, modified to include Allen's area computations.

pelvic disproportion, and should serve to stimulate more precise evaluation of the classification, essential diameters, and areas in square centimeters, of each plane of the pelvis.

Midpelvic contractions, if present, should be suspected, even in the presence of normal inlet and outlet measurements; and these cases should merit the advantages offered by stereo- and isometric roentgenpelvimetry. If clinical measurements of this plane are found to be critical, significant midpelvic disproportion is highly possible.

Election of the proper procedure for the termination of the full-term pregnancy, and prediction of the course of labor may be made with a reasonable degree of accuracy.

With an average size baby, in the absence of unequivocal cephalopelvic disproportion, and under the "permissive" conditions outlined above in respect to the degree and nature of contraction, the patient may, under careful supervision, be allowed to go into labor spontaneously.

No single diameter, except possibly the conjugate vera, should be employed alone for the prognosis of labor.

In considering the sums of any two diameters, that of the widest possible transverse diameter and the anteroposterior diameter might well be combined with the area computation for the fullest measure of efficiency. The latter consideration, emphasizing the presence or limitation of compensatory space, proves the importance of stereo-perspective and classimetric knowledge of the particular pelvis; and appears more significant than a study of the sum of the interspinous and posterior sagittal diameters.

The proper clinical roentgenometric approach to the suspect pelvis promises a favorable advance in lessening maternal morbidity and mortality, a greater fetal salvage, and a lesser incidence of elective cesarean section.

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Criticism for resorting to elective cesarean section for suspected contracted pelves in ten cases with an inlet sum of 22.72 cm. (baby's weight 3,300 Gm.), another with a sum of 23.90 cm. (3,370 Gm.), and five cases with a sum of 26.30 cm. (3,587 Gm.), is likely justified. In those instances of unengaged heads at term, with an inlet mean diameter of 9.39 cm., and a combined anteroposterior and transverse of 22.18 cm., a cesarean section was justifiably indicated.

In this group of patients there were three placenta previas, three with a history of previous sections, one deformed pelvis, one antenatal rupture of the uterus (endometriosis), and five toxemias. There was one stillborn fetus. Although the fetus weighed only 2,300 Gm., the pelvis was one of severe just minor type.

Our experience is in agreement with the impression of Weinberg and Scadron, and of Guerriero, in respect to the critical midplane sums of 13.0 and 13.5 cm., as indicated in sections I-C, II-C, and III-C of Table IV. It is important to state, perhaps, that these patients were delivered as soon as dilatation was complete. Of late, the incidence of midforceps application has been materially reduced by the practice of giving minute doses of pituitrin at the time of delivery. The cases included in section IV-C might have been reduced to a low forceps termination in such manner. It is of significance that areas recorded in sections I-C and II-C were below the critical areas.

Axis traction was resorted to, in many cases, by reason of anticipating a more desirable directional force where traction with other types of forceps seemed a little forced. With our present knowledge, the cases indicated in section III-A (Table IV) could well be permitted a trial of labor. The patients shown in sections I-C, II-C, and IV-A suffered a definite arrest in labor. As will be noted, forty-six operative deliveries were experienced with a midplane sum of less than 13.0 cm., namely: 27 elective sections (3,375 Gm.); 2 intrapartum sections (3,964 Gm.); and 17 fairly difficult forceps deliveries (3,514 Gm.). However, three patients with a mean area of 83.8 sq. cm. (section I-D) delivered spontaneously of babies with a mean average weight of 3,173 Gm. In this series there was only one stillbirth encountered, and in no instance was there any significant maternal or permanent fetal injury sustained. One may readily understand the reasons for spontaneous outcome in sections I-D, III-D, IV-D, and V-D. The sums of the anteroposterior and the interspinous diameters ranged from 23.54 cm. to 20.36 cm. in the operative cases. The real critical level appears to be about 21.5 centimeters. The critical area values of 81.0 sq. cm. (3,500 Gm.) to 91.0 sq. cm. (3,600 Gm.) agree favorably with those in Allen's critical range.

Some difficulty was met with midplane sum means of 13.53 cm., 14.30 cm., and 15.63 cm. (babies of 3,585 Gm., 3,456 Gm., and 3,687 Gm.). In these instances, other factors, such as moldability, poor uterine contractions, and interference early in the second stage of labor may have been in force. The mean areas were 85.9 sq. cm., 102.0 sq. cm., and 107.2 sq. cm. One may summarize that the critical level remains between 13.0 cm. and 13.5 cm., and the critical area about 90.0 sq. cm. for a 3,300 to 3,600 Gm. baby.

Knowledge gained from surveys of this type should prove very helpful in evaluating the clinical-suspect pelvis, and in exercising the proper conduct of labor in the particular case. A consideration of the importance of the widest transverse diameter in conjunction with the anteroposterior diameter as concerns the midplane (compared to the sum of the latter and the interspinous measurement) is now being conducted in current studies. It is anticipated that the incidence of operative deliveries, to include cesarean sections, will be further reduced.

Summary

Precision obstetrics is within the scope of practicability. A careful survey of the female pelvis allows for recognition of absolute or relative cephalo-

majority of the cervical amputations alone were in old women with apparently normal uteri for their age; in all cases a thorough curettage was done to see if pathology might be present and the uterus was left in place to give better pelvic support.

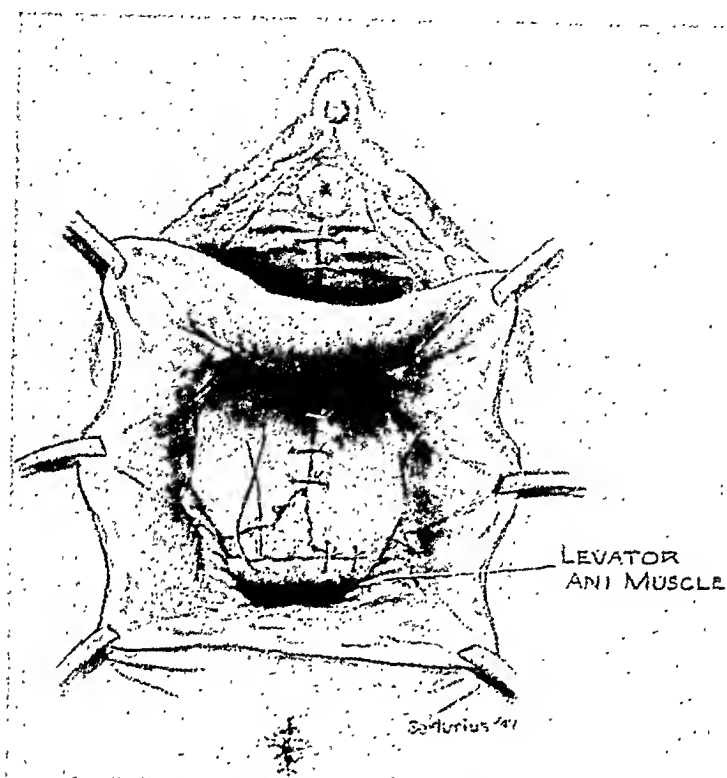


Fig. 5.—Radical repair of rectocele. The areolar fascia of posterior wall of vagina has been exposed and longitudinal split is being sutured and the transverse split of fascia with the fascia of the triangular ligaments being brought together.

TABLE VI

| POSTOPERATIVE COMPLICATIONS | NUMBER | PER CENT |
|-----------------------------|--------|----------|
| Pyelitis | 20 | 6.6 |
| Cystitis | 18 | 6.0 |
| Mild vaginal bleeding | 11 | 3.6 |
| Perineal wound infections | 10 | 3.0 |
| Shock | 3 | 1.0 |
| Thrombophlebitis | 3 | 1.0 |
| Pneumonia | 2 | 0.6 |

There were no hospital deaths in this unselected series of 300 cases, and the complications produced by infection responded readily to sulfa and other therapy. The three cases of thrombophlebitis were mild, one not appearing until the twenty-first postoperative day and no anticoagulants or vein ligation were necessary.

The most consistent findings were chronic cervicitis and uterine vascular changes associated with the prolonged congestive state of the pelvic structures.

The three cases of carcinoma of the cervix were not suspected before operation and were followed with deep x-ray therapy. One patient with car-

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TECHNIQUES FOR ISOLATION, MAINTENANCE, AND MASS CULTURE OF DÖDERLEIN'S BACILLUS*

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SINCE the initial observations regarding the incidence of gram-positive rods in the vagina and the description of these bacteria by Döderlein,¹ a group of organisms now referred to as "Döderlein's bacillus" has come to be used in clinical parlance as one criterion of normality of the human vagina. As such, these bacteria occupy a unique position. Since the low pH of the vaginal fluids in a clinically normal woman has been attributed by Cruickshank and Sharman,² Cruickshank,³ Rakoff⁴ to the metabolism of this organism, the solution of numerous problems in its physiology becomes of paramount importance both to the gynecologist and the physiologist, not to mention workers⁵⁻⁷ in the field of endocrinology. There remains an open question regarding the precise role of these gram-positive rods in establishing and maintaining the low pH (4.0 to 5.5) of the so-called "normal" vagina. These problems may well be resolved in part by attempts to study the physiology of the organism in pure culture.

Unfortunately, workers^{8,9} in this field have encountered difficulty in isolating these bacteria from mixed cultures and maintaining them for an extended time on any of the known media combinations.

Cruickshank¹⁰ proposed the use of lactose or glucose hormone agar with 5 per cent defibrinated rabbit blood for the primary isolation of the Döderlein bacilli. It was relatively easy for him to isolate this organism when a Grade I flora existed. However, he encountered difficulty in isolating the bacillus in the mixed culture of a Grade II flora.

Brown and Redowitz¹¹ adopted whey agar for isolating and maintaining cultures of the vaginal bacillus. The organisms grew poorly at first but apparently adapted themselves to this medium after frequent transfers.

Tomato juice agar, a medium described by Kulp,¹² has given favorable results for the isolation of *Lactobacillus acidophilus*. Weinstein et al.¹³ added yeast extract to this medium for the isolation of Döderlein's bacillus.

The purpose of this study was to find an improved medium which would successfully maintain these vaginal bacilli in prolonged culture and provide a possible harvest of mass cultures. It was felt that, if this could be accomplished, the first step toward a program of investigation leading to an understanding of these gram-positive rods and their relation to their natural habitat would have been accomplished.

*The author is greatly indebted to Dr. Mortimer Speiser and Dr. Heinz Luschinsky of Bellevue Hospital for their assistance in obtaining vaginal cultures.

The blood serum used in this study was obtained through kindness of the staff of the State of New Jersey Department of Health, Trenton, New Jersey.

Materials

Nine cultures were included in this study. Five of these were isolated from patients in the gynecology clinics at Bellevue Hospital and at the Ortho Research Foundation. The four remaining cultures were obtained from Dr. Robert A. Hart,* and from the American Type Culture Collection.

I. Culture No. 9478. Isolated after completion of treatment for trichomonas vaginalis vaginitis. A clinically normal vagina and a Grade I flora by direct smear existed at the time of isolation.

II. Culture P. Obtained from a clinically normal vagina with no history of vaginitis. A Grade I flora was evident by direct smear and culture.

III. Culture R. Isolated following treatment for a trichomonas infection. The vagina was trichomonad free and clinically normal. Upon culture for Döderlein's bacillus, fourteen additional vaginal organisms of different morphology were isolated, although the direct smear indicated a Grade I flora.

IV. Culture W. The patient was in the first trimester of pregnancy. An abundance of Döderlein's bacillus was evident in both the direct smear and culture.

V. Culture H. A clinically normal vagina and a Grade I flora were indicated in the direct smear and by culture.

VI. *Lactobacillus acidophilus* No. 9857. This culture was also listed as "Döderlein's bacillus" and was obtained from the American Type Culture Collection.

VII. *Lactobacillus acidophilus* No. 4357. American Type Culture Collection.

VIII. *Lactobacillus acidophilus*, strain "A." According to Dr. Hart, this strain was isolated from soured milk over twenty years ago.

IX. *Lactobacillus acidophilus*, strain "M." The origin of strain "M" is not known. It was originally obtained from Dr. John Torrey and was sent to us by Dr. Hart.

Methods

Development of a Medium.—The technique employed for obtaining Culture No. 9478 was as follows. A patient was placed in the lithotomy position. The labia were separated manually and a sterile speculum was inserted. Cultures were taken from the posterior fornix with sterile swabs. With the first swab, a direct smear was made by rolling the swab on a sterile slide. The remaining swabs were expressed into beef heart infusion broth (Difco), acetic acid broth, thioglycollate broth (B.B.L.)† with 10 per cent human serum added, and cysteine-peptone-liver-maltose medium.¹⁴ Dextrose was added in a 1 per cent concentration to each broth medium since Cruickshank⁸ established a requirement for a fermentable carbohydrate.

Each of these broth cultures was immediately streaked in duplicate on 1 per cent dextrose agar, dextrose agar with sodium oleate, dextrose blood agar, trypsin digest agar, tomato juice agar,¹² and Weinstein's tomato-milk agar.¹³ One set of streaked plates was incubated in a Brewer's anaerobic jar while the other set was incubated under 10 per cent carbon dioxide tension as outlined on page 7 of *Standard Methods*.¹⁵

With the exception of the thioglycollate serum broth, none of the above broth media provided any gram-positive rods after twenty-four hours' incubation at 37° C. This was possibly due to overgrowth by other vaginal bacteria. The solid media streaked initially from these broth media gave a scant growth of pinpoint colonies, after forty-eight hours' incubation at 37° C. with the exception of trypsin digest agar. This initial streak culture on solid media before incubation of the broth was, therefore, abandoned in subsequent attempts at isolation. The thioglycollate serum broth, which supported a mixed

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†Baltimore Biological Laboratory.

culture, including gram-positive rods after incubation, was plated in duplicate on Kulp's tomato juice agar and Weinstein's tomato-milk agar and incubated for forty-eight hours at 37° C. both anaerobically and under 10 per cent carbon dioxide tension.

Although colonies of other organisms were found on both these solid media, it was not difficult to detect pure colonies of gram-positive bacilli in anaerobic culture and under carbon dioxide tension. These colonies of gram-positive organisms were slightly larger on the Weinstein's tomato-milk agar plates. Therefore, the latter medium was selected as the temporary medium for carrying these purified cultures. However, the cultures on this solid medium and in thioglycollate serum broth died off after several weeks of serial culture. Consequently, a search was started for both a broth medium and a solid medium for sustained culture following isolation from thioglycollate serum broth.

On the next attempt, Culture P was successfully isolated from thioglycollate broth. It was found that improved colony growth on the tomato agar media was obtained if the surface was initially flooded with a very thin layer of thioglycollate serum broth.

Culture P was sustained successfully when a substrate combination including all of the ingredients of thioglycollate serum broth and Weinstein's tomato-milk agar was used. The ingredients of these two media are listed in Tables I and II.

TABLE I. WEINSTEIN'S TOMATO-MILK MEDIUM

| | |
|-----------------------|----------|
| Filtered tomato juice | 200 c.c. |
| Peptone | 5 Gm. |
| Peptonized milk | 10 Gm. |
| Yeast extract | 5 Gm. |
| Agar | 20 Gm. |
| Distilled water | 800 c.c. |

TABLE II. THIOGLYCOLLATE SERUM BROTH

| | |
|-------------------------------|-------------|
| Peptone (trypticase, phytone) | 20 Gm. |
| Dextrose | 10 Gm. |
| Sodium chloride | 5 Gm. |
| Dipotassium phosphate | 2 Gm. |
| Sodium thioglycollate | 1 Gm. |
| Methylene blue | 0.002 Gm. |
| Agar | 0.5 Gm. |
| Distilled water | 1,000 c.c. |
| Serum (human) | 10 per cent |

The total concentration of peptone in the completed B.B.L. thioglycollate broth was 2 per cent. Of this amount, 12.5 per cent is phytone and the remaining peptone is trypticase.

At this point, a variety of media combinations containing the various ingredients of the above combined thioglycollate-tomato juice medium were tried in order to eliminate nonessential components.

Colony size on an agar surface and sustained growth were the criteria for the effectivity of these media combinations.

In the course of this work it was definitely established that serum and dextrose were required for sustained growth. Therefore, 10 per cent human serum, 1 per cent dextrose, and 1.5 per cent agar were used as a basal medium to which the separate ingredients of the thioglycollate-tomato milk combination were added.

The addition of phytone to the basal medium produced a more prolific growth of colonies. Upon increasing the concentration of phytone, a definite increase in colony size was observed. Optimal growth was obtained with 2 per cent phytone in the final medium. The other ingredients were demonstrated as unimportant and were therefore abandoned.

The formulation of the optimal medium is as follows:

| | |
|------------------|---------|
| Phytone (B.B.L.) | 2 Gm. |
| Dextrose | 1 Gm. |
| Distilled water | 90 c.c. |
| Serum (human) | 10 c.c. |

The phytone and dextrose are dissolved and the medium tubed in 9 c.c. amounts. After autoclaving at 15 pounds pressure for fifteen minutes the medium is allowed to cool and 1 c.c. of sterile serum is added to each tube. The serum is adjusted to pH 6 with N/1 HCl and sterilized by filtration. The pH of the final medium varies between 6.1 and 6.5. This medium has been given the name P.D.S. medium (phytone, dextrose, serum). The addition of 1.5 Gm. of agar to the fluid medium before autoclaving provides a solid medium for plate culture.

Broth cultures using P.D.S. medium produced heavy growth of the gram-positive bacillus in twenty-four hours at 37° C. Subsequent isolations of the Döderlein organism from patients with either a Grade I or Grade II flora were readily accomplished with this medium.

The procedure employed was as follows: The vaginal swabs were expressed into P.D.S. broth medium and incubated for twenty-four hours at 37° C. After incubation, the gram-positive rods grew profusely, while the majority of other vaginal organisms present from a Grade II flora were either inhibited or killed by the acidity produced by the rapid growth of Döderlein's bacillus. To isolate the organisms in pure culture, these incubated P.D.S. broth cultures were streaked on the P.D.S. agar medium and incubated anaerobically for forty-eight hours at 37° C. Isolated colonies were picked from the solid medium into P.S.D. broth. Several transfers were carried in the broth medium before being seeded into the following stock culture medium.

The medium devised for maintaining stock cultures was Difco litmus milk medium with 1.5 per cent phytone added. Three hundredths of 1 c.c. of the broth culture was seeded into the litmus milk-phytone medium and incubated for twenty-four hours at 37° C. and then stored in the refrigerator. Transfers were successfully made after three or four weeks storage.

Cultural Characteristics and Biochemical Reactions

Cell Morphology.—The gram-positive Döderlein organisms vary in length and thickness. They are either straight or curved rods, appearing singly or in short and long chains. The ends may be flat or rounded. All forms change, depending on the age of the culture and the nature of the culture medium.

The photomicrographs show a resemblance between the vaginal bacilli and *Lactobacillus acidophilus*. Cultures P and H which are gram-positive rods occurring singly resemble *L. Acidophilus*, strain "A." Whereas, cultures W, R, and 9857 appear to be morphologically similar to *L. acidophilus*, strain "M."

Colony Morphology.—The colony growth of the Döderlein organism on P.D.S. agar medium is punctiform to circular. Isolated colonies are cream colored and opaque with a transparent edge. A large mass of colonies appears

to have a foamy, white surface. The younger colonies are of a soft consistency which, upon aging, become slightly dry and mealy. In the presence of serum, the colonies become surrounded by an aerola of turbid agar.

Anaerobiosis is necessary for initial culturing of this organism, but after several transfers the vaginal bacillus will grow aerobically. However, reduced oxygen tension is recommended for larger colonies and more rapid growth of the adapted strains.

Several strains of *Lactobacillus acidophilus* have been included in this study (see list of cultures studied) for the purpose of determining whether or not *L. acidophilus* colonies can be differentiated from Döderlein's bacillus on the P.D.S. agar medium. Morphologically, it is impossible to distinguish a *Lactobacillus acidophilus* colony from a colony of Döderlein's bacillus.

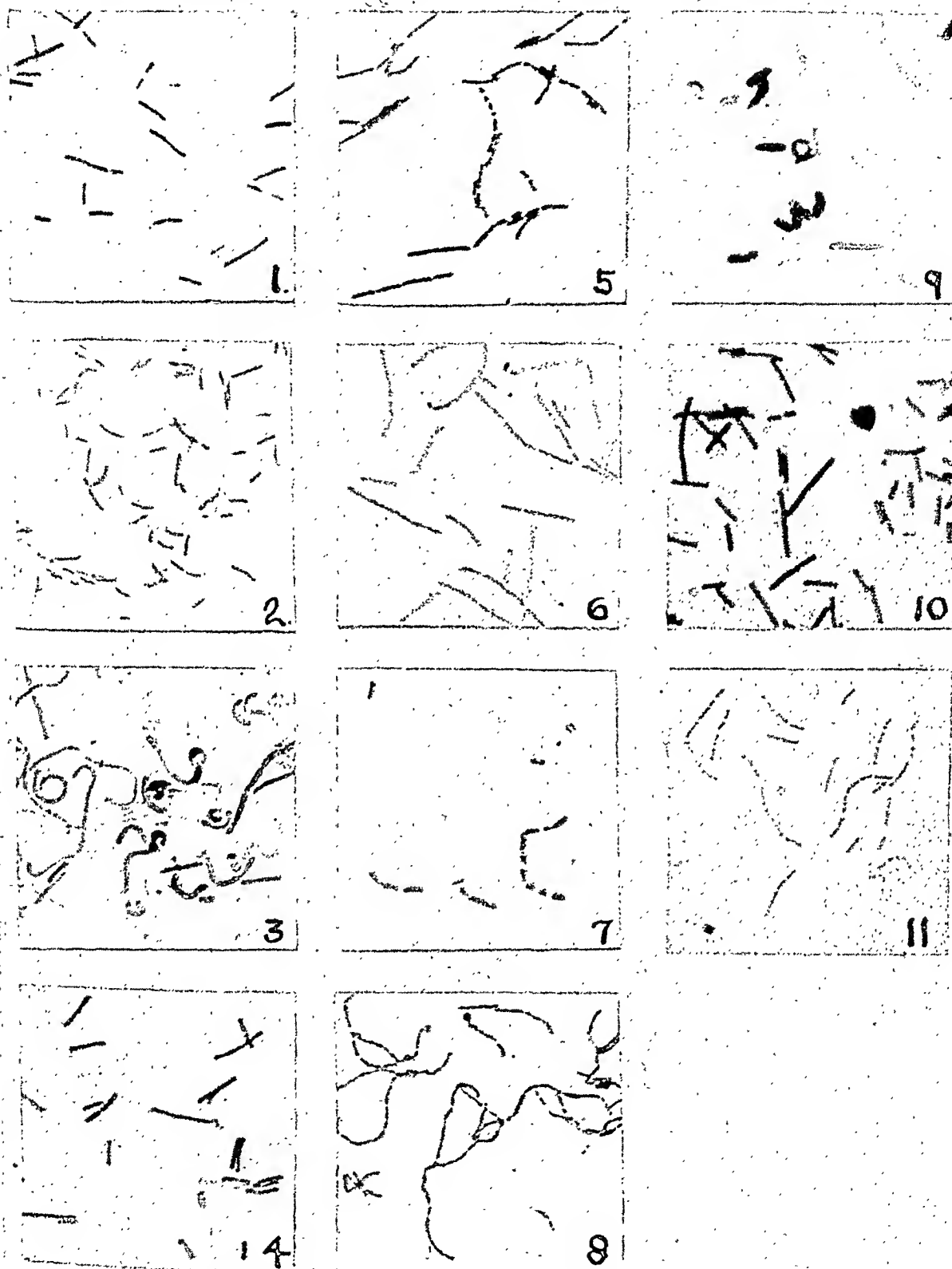
Broth Cultures.—The uninoculated P.D.S. broth medium had a clear brownish-red color. With the growth of Döderlein's bacillus or *L. acidophilus*, the medium became very turbid. There was no surface growth produced by either of these cultures, although a heavy, compact, grayish-white sediment developed after 24 hours. Upon aging, heavy growth was noticeable along the sides of the broth tubes. Any odor due to the bacteria was masked by the odor of the phytone.

Litmus Milk Reactions.—Cultures of Döderlein's bacillus and *Lactobacillus acidophilus* inoculated into Difco litmus milk gave slow, unreliable reactions. However, with the addition of 1.5 per cent phytone to litmus milk, an acid curd, complete reduction, and peptonization developed in twenty-four to forty-eight hours. The exceptions to this statement were Culture W and *Lactobacillus acidophilus*, strain "A." These two cultures required nine to fourteen days to produce a curd, although an acid reaction and complete reduction occurred in twenty-four to forty-eight hours. These reactions have been found to be consistent and reliable in the presence of phytone.

TABLE III. COMPARISON OF CARBOHYDRATE FERMENTATION REACTIONS

| | CULTURE R | CULTURE 9857 | CULTURE P | CULTURE W | CULTURE II | L. ACID 4357 | L. ACID "M" | L. ACID "A" |
|------------|--------------|-----------------|--------------|--------------|---------------|-----------------|----------------|----------------|
| Sorbitol | — | — | — | + | + | + | + | + |
| Raffinose | — | + | — | + | + | + | + | + |
| Rhamnose | — | — | — | + | + | + | + | + |
| Melezitose | + | + | — | + | + | + | + | + |
| Melibiose | + | — | — | + | + | + | + | + |
| Galaetose | + | + | + | + | + | + | + | + |
| Levulose | + | + | + | + | + | + | + | + |
| Mannite | — | — | + | + | + | + | + | + |
| Maltose | + | + | + | + | + | + | + | + |
| Adonitol | — | — | — | + | + | + | + | + |
| Cellobiose | + | + | + | + | + | + | + | + |
| Glycogen | + | + | + | + | + | + | + | + |
| Arabinose | + | + | — | + | + | + | + | + |
| Dextrose | + | + | + | + | + | + | + | + |
| Trehalose | + | + | + | + | + | + | + | + |
| Lactose | + | + | + | + | + | + | + | + |
| Glycerine | — | — | — | + | + | + | + | + |
| Mannose | + | + | + | + | + | + | + | + |
| Sucrose | + | + | + | + | + | + | + | + |
| Xylose | — | — | — | + | + | + | + | + |

Carbohydrate Fermentation Reactions.—Döderlein's bacillus will not grow well in ordinary culture media, therefore phytone medium without dextrose and with 5 per cent serum was used as a basal medium for fermentation



Comparison of Döderlein's bacillus and related organisms ($\times 1,200$).

Fig. 1.—Culture P, twenty-four hour P.D.S. broth culture; Fig. 2.—Culture P, twenty-four hour P.D.S. agar culture; Fig. 3.—Culture P, one week P.D.S. agar culture; Fig. 4.—Culture P, twenty-four hour thioglycollate-tomato milk agar culture. The following are twenty-four hour P.D.S. broth cultures: Fig. 5.—Döderlein's bacillus No. 9857; Fig. 6.—Culture H; Fig. 7.—Culture W; Fig. 8.—Culture R; Fig. 9.—*L. acidophilus* No. 4357; Fig. 10.—*L. acidophilus* "A"; Fig. 11.—*L. acidophilus* "M."

reactions. This mixture was known in itself to contain fermentable carbohydrates. However, phytone and serum without added carbohydrate permitted only a barely visible growth at the bottom of the tube. This growth did not increase on prolonged incubation, whereas, with the addition of 1 per cent dextrose, a heavy sediment and turbidity occurred. This turbidity, accompanied by a definite lowering of pH, was taken as indicative of a positive reaction.

The carbohydrate to be tested was prepared in 10 per cent solution and sterilized by autoclaving at 15 pounds pressure for fifteen minutes. The sterile solution was then added aseptically to make a 1 per cent solution in the final tubed medium. Three hundredths c.c. of a saline suspension from a washed twenty-four hour P.D.S. agar slant culture was pipetted into each tube. The results of the carbohydrate fermentation reactions are shown in Table III.

As seen in Table III, *L. acidophilus* could not be differentiated from the gram-positive bacilli isolated from Culture W and Culture H. The stock Culture No. 9857 and the gram-positive rods isolated from Cultures R and P gave variable reactions which did not permit any general conclusions to be drawn.

Thermal Death Point of Culture P.—Eight c.c. amounts of P.D.S. broth were placed in a constant-temperature water bath for approximately one-half hour to warm the tubes to the experimental temperature. Each tube was then inoculated with 0.03 c.c. of a twenty-four-hour P.D.S. broth culture. Following inoculation, the tubes were immediately returned to the water bath. At intervals of two, three, four, five, ten, fifteen, twenty and thirty minutes, the tubes were removed and subcultures were made by pipetting 0.03 c.c. into P.D.S. broth medium which had been maintained at room temperature. Both sets of tubes, the original cultures removed from the water bath and the subcultures, were incubated for one week at 37° C. The experimental temperatures ranged from 45° to 74° C. For temperature ranges over 56° C., serum was added to the tubes after cooling to room temperature. The results given in Table IV summarize results for temperatures above 66° C.

Other Biochemical Reactions.—Such reactions as Indol and hydrogen sulfide formation and the Voges-Proskauer reaction were unreliable, due to masking by the deep red color of the P.D.S. medium.

TABLE IV. THERMAL DEATH POINT FOR TEMPERATURES ABOVE 66° C., CULTURE P.

| TEMPERATURE | MINUTES | | | | | | | |
|-------------|---------|---|---|---|----|----|----|----|
| | 2 | 3 | 4 | 5 | 10 | 15 | 20 | 30 |
| 66° C. | + | + | + | + | + | + | + | + |
| 69° C. | + | + | + | + | + | + | + | + |
| 72° C. | + | + | + | + | + | + | — | — |
| 74° C. | + | + | + | + | + | + | — | — |

Serologic Reactions.—Phytone-dextrose-serum broth was found to be an unsuitable medium in which to obtain antigen for agglutination tests. The acidity produced by the organism caused a precipitation of the protein material in the medium. Repeated washings did not separate all the protein material from the bacteria. Furthermore, the antigenic properties of the strains under study were found not to remain constant on the P.D.S. solid medium. Therefore, no clear-cut serologic differentiation could be made between the strains of Döderlein's bacillus and the strains of *Lactobacillus acidophilus* through agglutination tests.

Discussion

Phyton is an enzymatic digest of soy beans, cotton seeds and peanut meal. The pH of various lots received in this laboratory varied between 6.1 to 6.5. Phytone contains a considerable amount of fermentable carbohydrates, including hexose sugars. It has an appreciable sulfur content, including cysteine. Hydrogen sulfide reactions are observed with lead acetate paper when *Eberthella typhosa* is grown in it. Phytone also contains thiamine, riboflavin, nicotinic acid, and pantothenate. The total nitrogen content is approximately 9.8 per cent and ash 6.4 per cent.¹⁶

The P.D.S. medium is a valuable aid for the isolation and maintenance of Döderlein's bacillus. However, there are indications for a refinement of this medium in order to permit reliable serologic and biochemical differentiations of the various strains encountered.

It is of interest to note that the "complete" chemically defined medium of Sprince and Kupferberg¹⁷ did not sustain growth of these gram-positive bacilli when serum, dextrose, and Wilson's solubilized liver were added to the medium.

Summary

1. A fluid medium providing optimal growth of Döderlein's bacillus in mass culture has been developed.

2. A solid medium has been devised, using the fluid medium as a substrate.

3. A procedure for successful isolation of Döderlein's bacillus is recorded.

4. The addition of phytone to Bacto litmus milk is recommended for the maintenance of stock cultures.

5. Döderlein's bacillus could not be differentiated from *Lactobacillus acidophilus* through carbohydrate fermentation and litmus milk reactions.

6. The thermal death point for one culture is recorded as 72° C. for twenty minutes in the absence of blood serum.

7. Biochemical and serologic differentiations cannot be made until the culture medium is further refined.

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A COMPARATIVE STUDY OF THE EFFICACY OF CERTAIN DRUGS IN PROMOTING EVACUATION OF THE FEMALE BLADDER FOLLOWING GYNECOLOGIC OPERATIONS*

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A NUMBER of studies have been carried out in recent years involving the problem of urinary retention after operation. Therapeutic agents have been made available from time to time with physiologic properties ascribed to them that seem difficult to reproduce clinically. Instillation of mercurchrome solution into the bladder at the time of operation has achieved more prominence than any other agent.

On the ward service of the Division of Gynecology, Department of Obstetrics and Gynecology at the Jefferson Medical College Hospital, when suggestive measures failed to promote spontaneous bladder evacuation, a "bladder laxative" was formerly employed. This consisted instilling 30 c.c. of sterile glycerin into the distended bladder by catheter, and then withdrawing the catheter immediately. This procedure was successful with a certain number of patients, but the method has more or less fallen into disuse in recent years, although it is still employed occasionally.

The present study was undertaken in an effort to determine the efficacy of various types of medication designed to decrease the number of catheterizations following gynecologic operations.

Catheterization after operation or the introduction of an indwelling catheter has definite disadvantages, and any type of therapy that will reduce the incidence of catheterization or preclude the use of the indwelling catheter is certainly desirable.

The array of therapeutic agents used in this connection further emphasizes the fact that none of the agents in use is always entirely satisfactory.

The investigation carried out comprises a comparative study of five series of patients, one a control, and four series in which different medicaments and methods were used, as follows:

1. One hundred in whom no medication was employed.
2. One hundred in whom mercurchrome was instilled into the bladder at the time of operation.
3. One hundred in whom aeriflavine was instilled into the bladder at the time of operation.
4. One hundred in whom prostigmine methyl sulfate was injected hypodermically prior to operation and also after operation.
5. Twenty-two in whom "Doryl" was injected hypodermically after operation.

*Read at a meeting of the Philadelphia Obstetrical Society, Dec. 4, 1947.

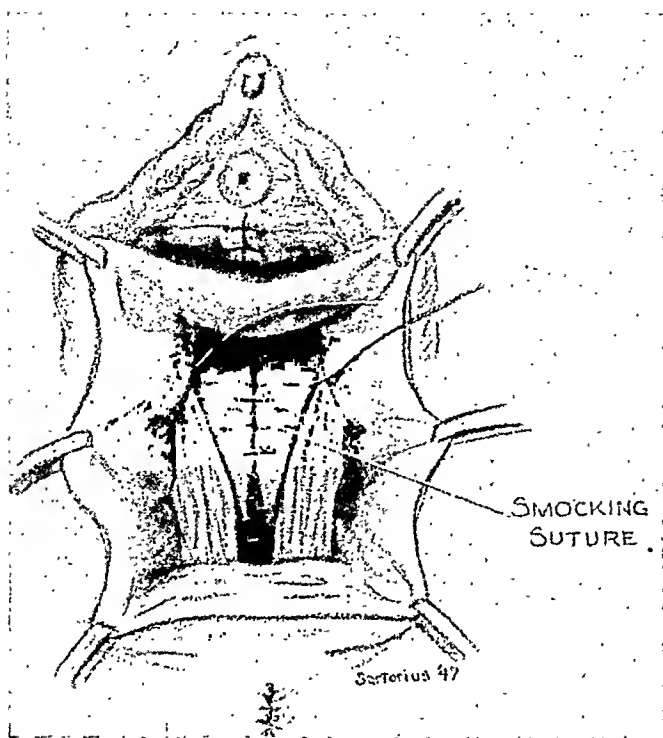


Fig. 6.—Radical repair of rectocele. Transverse laceration of triangular ligament has been approximated and redundant fascia of posterior vaginal wall is being plicated by smocking suture to close weakness of walls and to reinforce pelvic floor with fascial planes.

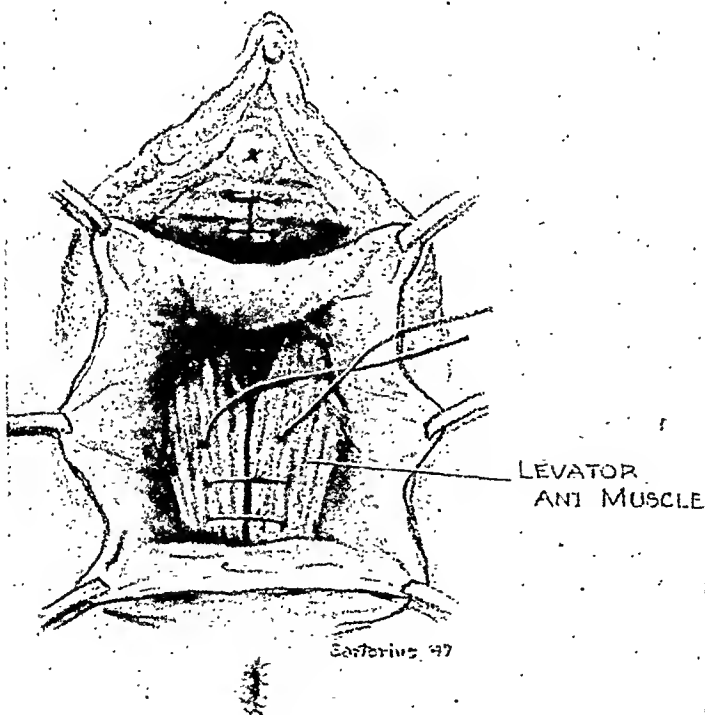


Fig. 7.—Radical repair of rectocele. The split edges of the fascial planes have been approximated and plicated and the levator ani muscles loosely approximated with catgut sutures. Mucous membranes are approximated with interrupted catgut and skin edges with subcuticular stitch of chromic catgut. At completion of operation, rectum dilated manually to admit three fingers.

were catheterized. Acriflavine (1 to 1,000) was used initially in a small group of the patients in this series, but this seemed to cause a rather marked degree of bladder irritability, frequency, and tenesmus. Using a 1 to 2,000 solution later on, we had less trouble, although a certain number still developed frequency and tenesmus. Sixty-one patients of the one hundred patients in this series were catheterized in this group (Table III).

TABLE III. ACRIFLAVINE SERIES

| TYPE OF OPERATION | NUMBER OF PATIENTS | NUMBER CATHETERIZED | PER CENT CATHETERIZED |
|-------------------------------|--------------------|---------------------|-----------------------|
| Abdominal section | 66 | 35 | 53.0 |
| Plastic | 22 | 16 | 72.7 |
| Plastic and abdominal section | 12 | 10 | 83.3 |
| Total | 100 | 61 | 61.0 |

Prostigmine Methyl Sulfate Series

In the fourth series 1 c.c. of a 1 to 1000 solution of prostigmine methyl sulfate was injected hypodermically twelve, six, and three hours prior to operation; 1 c.c. was also injected six, nine, fifteen, and twenty-one hours after operation.

In subdividing these cases we find that 58.6 per cent of the patients having abdominal sections were catheterized at least once, while 100 per cent of those having plastic procedure and 66.6 per cent of those having a plastic and section were catheterized.

TABLE IV. PROSTIGMINE METHYL SULFATE SERIES

| TYPE OF OPERATION | NUMBER OF PATIENTS | NUMBER CATHETERIZED | PER CENT CATHETERIZED |
|-------------------------------|--------------------|---------------------|-----------------------|
| Abdominal section | 75 | 44 | 58.6 |
| Plastic | 13 | 13 | 100.0 |
| Plastic and abdominal section | 12 | 8 | 66.6 |
| Total | 100 | 65 | 65.0 |

Sixty-five per cent of the hundred patients in this series were catheterized (Table IV).

"Doryl" Series

In the final series of patients studied, 1 c.c. Doryl was used postoperatively by hypodermic injection, upon patients who could not void voluntarily.

While no untoward reactions were observed in any of the patients in this series, we were aware of some patients who had previously had reactions to the drug, and therefore were not comfortable about its use. The drug was used in 22 patients who could not void, and it was successful in twelve (54.5 per cent). We do not feel that the results were sufficiently impressive to warrant continued use of the drug in a larger number of patients.

Reference to the composite Table V would indicate that mercurochrome was the most effective type of medication used. While only 37.0 per cent of the total number were catheterized, 70.0 per cent of those having a plastic and abdominal section required catheterization. Mercurochrome did not seem to be as effective in our series as in Woodruff and Te Linde's, however.

In addition to these serial studies, cystometric studies were performed on a group of supposedly normal women (nonoperative cases) before and after the use of instillations of mercurochrome, acriflavine, and prostigmine methyl sulfate by injection.

Control Series

The first group of patients studied were those in whom we did not employ any type of medication in an attempt to induce micturition, other than the suggestive measures usually employed in trying to aid the patient to void. Seventy-seven per cent of this series were catheterized.

TABLE I. CONTROL SERIES

| TYPE OF OPERATION | NUMBER OF PATIENTS | NUMBER OF CATHETERIZED | PER CENT CATHETERIZED |
|--------------------------------|--------------------|------------------------|-----------------------|
| Abdominal section | 44 | 27 | 61.3 |
| Plastics | 30 | 27 | 90.0 |
| Plastic and abdominal sections | 26 | 23 | 88.4 |
| Total | 100 | 77 | 77.0 |

In analyzing this series we find that 61.3 per cent of those having sections were catheterized at least once, while 90.0 per cent of the plastic cases and 88.4 per cent of those having a plastic and section were catheterized. (Table I.)

Mercurochrome Series

The second group studied were those in whom mercurochrome was used. Fifteen cubic centimeters of a 0.5 per cent solution of mercurochrome were instilled into the patient's bladder after catheterization at the time of operation.

TABLE II. MERCUROCHROME SERIES

| TYPE OF OPERATION | NUMBER OF PATIENTS | NUMBER CATHETERIZED | PER CENT CATHETERIZED |
|-------------------------------|--------------------|---------------------|-----------------------|
| Abdominal section | 56 | 14 | 25.0 |
| Plastic | 34 | 16 | 47.1 |
| Plastic and abdominal section | 10 | 7 | 70.0 |
| Total | 100 | 37 | 37.0 |

The highest percentage of catheterizations (70 per cent) was among those having plastic and sections. Of the plastic procedures alone catheterization was necessary in 47.1 per cent, while only 25 per cent having abdominal sections were catheterized. Thirty seven per cent of the entire series in this group were catheterized. Two patients in this series developed hematuria, and several complained of unusual tenesmus (Table II).

Acriflavine Series

In the third series, 15 c.c. of a 1 to 2,000 solution of acriflavine were instilled into the bladder prior to operation, although a 1 to 1,000 solution was first used for awhile.

Eighty-three and three-tenths per cent of those having a plastic and section were catheterized, and 72.7 per cent of those having plastic procedures only were catheterized, and 53 per cent of those having abdominal section alone

acknowledged that the physiology of micturition has been interfered with, and perhaps various factors are involved at different times. Additional etiologic factors frequently mentioned are: length of operation, type of operation, type of anesthesia, psyche of patients, position of patient while attempting to void, postoperative medication, diminished sensibility of bladder mucosa, vegetative unbalance, lack of parasympathetic and overaction of sympathetic nerves.

Jordan carried out cystometric studies on dogs using pilocarpine, pituitrin, potassium citrate and atropine, all of which gave a marked increase in tonus except atropine. Pilocarpine was used in the human being in smaller dosage but only slight rise in pressure resulted; larger doses caused abdominal pain and profuse perspiration. Acetylcholine caused only slight rise in pressure, while potassium acetate given orally in a dilution of 1 to 15 caused a definite rise in bladder tonus. Cystometric studies were also performed by Gernon, Palmer, and McKenna using mecholyl and gynnergyn. Both of these drugs caused increased intra-cystic pressure in a different manner. The effect of mecholyl is obtained by causing a parasympathetic preponderance, while gynnergyn also causes parasympathetic predominance by inhibition of both the motor and inhibitory sympathetic endings.

Since retention of urine is noted in patients other than those having gynecologic operations, it would undoubtedly seem that several factors enter into the picture, rather than one. On the other hand since retention occurs so much more frequently after gynecologic operations, tissue trauma is probably the most important single factor. Operative procedures of any type, either on the vulva, the anterior or posterior vaginal walls, urethra, or cervix are more likely to cause retention than abdominal section alone.

In the course of abdominal section the parasympathetic nerves passing over the brim of the pelvis can easily be traumatized because of the prominence of the sacrum and the proximity of the presacral plexus. Pressure in this area by the operator's hand and also by packs can be sufficient to alter the physiology of these nerves.

Conclusions

1. Five series of patients, one a control series, were studied in order to determine the effect of therapeutic agents in overcoming postoperative bladder retention.

2. Instillation of mereurochrome, 15 c.c. of a 0.5 per cent solution, into the bladder at the time of operation was found to be most effective.

3. Cystometrically there was little, if any, change in the intra-cystic pressure before and after the use of mereurochrome and acriflavine, however, there was a slight rise in the case of the prostigmine.

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Discussion

DR. ROBERT A. KIMBROUGH.—The evaluation of any form of therapy for conditions which tend to right themselves spontaneously is indeed a difficult, if not an impossible matter. The need for catheterization "at least once" constitutes Dr. Lintgen's criterion

TABLE V. COMPOSITE CHART—FOUR SERIES

| | ABDOMINAL SECTION | PLASTIC | PLASTIC AND ABDOMINAL SECTION | TOTAL PER CENT CATHETERIZED |
|-----------------------------------|-------------------|----------------|-------------------------------------|-----------------------------------|
| Control series | 61.3 per cent | 90.0 per cent | 88.4 per cent | 77.0 per cent |
| Mercurochrome series | 25.0 per cent | 47.1 per cent | 70.0 per cent | 37.0 per cent |
| Acriflavine series | 53.0 per cent | 72.7 per cent | 83.3 per cent | 61.0 per cent |
| Prostigmine methyl sulfate series | 58.6 per cent | 100.0 per cent | 66.6 per cent | 65.0 per cent |

Patients requiring plastic and section as a whole required more catheterizations than did those having either plastic operations or abdominal sections, while in the abdominal sections alone fewer catheterizations were required than in plastic operations alone.

The series in which prostigmine methyl sulfate was used required the highest percentage of catheterizations in the total series, and there were no complaints or untoward local or general reactions afterward.

Acriflavine proved to be too irritating to the bladder mucosa to recommend its use. If used in stronger concentration than 1 to 2,000 it was uncomfortable. Too great an inference cannot be drawn from the groups having a plastic and section, since in each of these there was a relatively small number of patients; hence no definite conclusions should be drawn until a larger number of patients have been evaluated.

Discussion of Mode of Action

It is thought that the mode of action in the use of mercurochrome and also with acriflavine is through an irritative action upon the mucous membrane of the bladder; prostigmine methyl sulfate, however, acts by stimulating the parasympathetic nerves which cause the detrusor musculature to contract and the sphincter fibers to relax. Regardless of specific physiologic action, it would seem that an increase in bladder tonicity would be reflected in an observation of cystic pressure, and with this in mind cystometric studies were carried out on some patients with apparently normal bladders, both before and after the employment of the medicinal agents previously mentioned. These results were somewhat surprising, for they did not coincide with our clinical experience.

In five cystometric examinations made on such patients before and after the instillation of mercurochrome (15 c.c. of 0.5 per cent solution) there was practically no change observed in the intracystic pressure after the instillation of mercurochrome, from that noted beforehand.

Using acriflavine (1 to 2,000 solution) proved results similar to those noted with mercurochrome.

We were surprised, however, in the use of prostigmine methyl sulfate (1 to 4,000 solution) given hypodermically one hour and two hours prior to the test, for in this instance constant, but not marked rise in intracystic pressure was noted.

These tests were made with a simple water manometer, and the recordings were expressed in centimeters of water and the findings for the normal intracystic pressure were similar to those reported by McLellan, namely, 1 to 8-15 cm. of water.

The causative factor in the postoperative retention of urine in gynecologic patients has been attributed grossly to trauma of the adjacent tissues. This is undoubtedly true to some extent, even though patients with other than pelvic operations frequently have retention of urine. Nevertheless, it is generally

indebted to Dr. Lintgen for bringing this recent work of his to our attention as a corrolary to his work in the past, and we have profited by the presentation and discussion.

DR. LINTGEN (Closing).—To answer Dr. Kimbrough's question about "Doryl." We did not have any adverse reactions, but we discontinued its use because of the unfavorable newspaper publicity about cases in which Doryl was used intravenously and several patients died. We discontinued using it at that time, and we have not used it since. Tidal drainage we do use and like it very much. Regarding Dr. Fetterman's question on early ambulation: this study was done prior to the time early ambulation was initiated, but I feel sure early ambulation will make patients void much more quickly after operation. These studies indicate that none of the drugs are too good, and as a result most of us at Jefferson Hospital use an indwelling catheter, especially for plastic cases, and practically in all of the sections. Some of us still use mereurochrome, but have abandoned the use of the other drugs.

of inadequate bladder function in this study. It would be interesting to have a further breakdown as to the number of catheterizations required in each group and the length of time over which catheterization was necessary. From his studies it would appear that the use of 15 c.c. of $\frac{1}{2}$ per cent solution of mercurochrome is superior to the other methods which he has utilized. In our hands instillation of any solution proved so disappointing that for the past several years we have utilized an indwelling catheter for twenty-four hours in simple cases, and for forty-eight hours in extensive plastic operations and in cases of total hysterectomy. It is my belief that the bladder, postoperatively, causes little concern except in those cases which have been subjected to a repair of the anterior vaginal wall. The slow return of normal bladder function is probably due to relatively poor hemostasis in anterior colporrhaphy. The bleeding usually comes from the sulcus underneath the descending pubic ramus where it is almost impossible to ligate every small vein. A small organized hematoma beneath the bladder neck probably interferes considerably with sphincteric function. It is suggested, therefore, we attempt to secure as near absolute hemostasis as possible before closure of the anterior vaginal wall.

When Dr. Lintgen closes the discussion I would like to know more about "Doryl," particularly the rationale of its use. I would like also to know what his experience has been with tidal drainage of the bladder which does not begin to function within a few days. On several occasions we have found the results of this method most gratifying. And, was there any less tendency toward retention after patients started to void, with one preparation or another?

DR. MARY D. PETTIT.—I would like to ask if there has been any difference in the ambulation time operative during the study. Dr. Scheffey brought out this point and we also have found our recent tendency to earlier ambulation has reduced the number of catheterizations markedly. I would like to say that at the beginning of the war period at the Albany Hospital mercurochrome was used routinely postoperatively in bladders. During the latter part of the war period I was not there and I do not know the exact statistical reasons why they stopped using it. I do know that there was much tenesmus and hematuria and those were two reasons for the discontinuance of the procedure as a routine.

DR. LEWIS C. SCHEFFEY.—Dr. Lintgen has shown great interest in this subject which he has pursued assiduously for many years by studying the behavior of the bladder both with respect to postoperative infection and to voluntary urination after gynecologic operations. I know that his persistent and meticulous study in these patients has been demonstrated in the careful tables that he has presented. It would seem from this study, as Dr. Kimbrough has said, that mercurochrome was the most effective of the agents used. That brings up the question as to how often and how consistently continuous drainage should be employed following gynecologic operations. Over a period of years one acquires certain beliefs, or rather certain peculiarities of action. One of the things that has found favor with me has been continuous drainage with intermittent irrigation ("Y" set), rather than with an indwelling catheter alone, although we now have the improved Foley catheter which is more suitable than the mushroom catheter for this purpose. When the nursing problem is difficult, continuous drainage for several days may be the better plan. However, when we have operated to correct cases of incontinence, and when a patient has not been able to hold her urine, continuous drainage may cause a certain amount of paresis of the bladder and urethra and we may thus contribute to the defeat of our procedure. My own practice, after operating upon patients with distressing incontinence by the plication method, is to have been relieved by single catheterizations, for there is an excellent psychological effect upon a woman who has been losing her urine for several years when she finds that she cannot urinate at all by herself.

DR. SCHEFFEY.—I wonder whether the increasing tendency toward early ambulation will not further voluntary voiding in these cases, although I do not like to allow a patient out of bed in two or three days after an extensive plastic procedure. I think that we are

0.003 per cent, which would represent the approximate incidence of simultaneous intrauterine and extrauterine pregnancy in all pregnancies. The incidence at the Mayo Clinic has been two cases in 13,527 deliveries, or 0.015 per cent.

Review of Case Reports in the Literature Since 1935

For the purpose of review for this paper, we studied the case reports which have appeared in the literature from Jan. 1, 1935, through February, 1947. During this time, seventy cases have been reported,^{1, 3, 6-52} including the two we are reporting herewith. One of the seventy cases was that of a lithopedion which the patient carried for twenty-six years,³ leaving sixty-nine cases of simultaneous intrauterine and extrauterine pregnancy which we studied, including the two we are reporting. Among these cases, there were some noteworthy facts. One of the pregnancies occurred in the ovary²⁹ and one was an interstitial ectopic pregnancy for which a hysterectomy was performed.⁵³ In two cases, the authors noted the existence of two corpora lutea of pregnancy,^{26, 53} indicating that, in these patients, there was a possibility of coexistent pregnancies. In sixty-two recorded instances, the right Fallopian tube was involved twenty-nine times, and the left Fallopian tube, thirty-three times. At the time of operation, the uterus was noted to be enlarged in thirty-seven patients; silence on the part of the surgeon does not mean that the uterus was not enlarged, for the uterus normally enlarges in the presence of an ectopic pregnancy. One patient had a mummified seven months' fetus which was obstructing the birth passage during labor. This was found when cesarean section was performed to deliver the live twin.⁴⁸

In the past, this condition has been considered to occur in the older age group.¹¹ Generally, we found this to be true. Of the sixty-nine patients included in our study, twelve (17.4 per cent) were under twenty-six years of age, twenty-one (30.4 per cent) were twenty-six to thirty years of age, seventeen (24.6 per cent) were thirty-one to thirty-five years of age, fourteen (20.3 per cent) were thirty-six to forty years of age, one was over forty years of age and the age of four patients (5.8 per cent) was unknown. Fifty-three patients (76.8 per cent) were twenty-six years of age or over.

The maternal mortality rate has been considered high. In 1940, the mortality rate for cases up to that time was 19 per cent.¹¹ In the group of cases we studied, which were reported from 1935 to the present, there was a report of one maternal death in sixty-nine cases, a rate of 1.4 per cent.

Heterotopic pregnancy occurs with greater frequency in the multipara than in the woman who has not had children. In our series, forty-eight patients (70 per cent) were multiparas, ten (14 per cent) were primiparas and in eleven cases (16 per cent) the parity was not known.

In fifty-four cases, the average duration of extrauterine pregnancy was estimated to be 7.7 weeks. Six cases were not included in this estimation because the pregnancy had continued so far beyond the first trimester that their inclusion would have overbalanced the estimate, and, in nine other cases, the duration of the ectopic pregnancy could not be estimated.

Of the six cases which were not included in the estimation of average duration of pregnancy, in four, the ectopic pregnancy reached term. In these four cases, two of the infants lived,^{21, 42} one died in the abdomen¹⁴ and one died after transabdominal delivery.²⁵ The fifth patient was operated on at seven and a half months' gestation and both fetuses died.³¹ The sixth patient was delivered of a live baby by cesarean section when the birth canal was found to be obstructed by a mummified seven months' ectopic fetus.⁴⁸ Of the

SIMULTANEOUS INTRAUTERINE AND EXTRAUTERINE PREGNANCY

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SIMULTANEOUS ectopic and intrauterine pregnancy is a comparatively uncommon condition of more than usual interest. The condition is sufficiently engaging to have arrested the attention of a few authors and to have been the subject of some excellent reviews. The purpose of this paper is to review clinically the cases which have been reported since 1935, to arrive at the approximate total number of cases which are known to date, since many of the earlier case reports are incomplete, and to report the cases which have been seen at the Mayo Clinic.

Incidence

The total number of cases reported through 1938 was 353, according to Ludwig.¹ This total was decided upon by him through a study of previous compilations of Gemmell and Murray,² Mathieu,³ Novak,⁴ and Bland and associates,⁵ and by adding seventeen cases which he found reported in the literature, plus three of his own. Since 1938, other authors^{6, 7} have studied the literature and discovered several cases which were previously not included in the totals. Mitra,⁶ in 1940, reported on seventeen cases and Sloat and Peterson,⁷ in 1938, reported on sixteen, including their own; however, since it was found that some of these had been reported on by other writers also, Mitra actually added four new cases, including his own, and Sloat and Peterson added eight new cases, thus giving a total of 365. We were able to find thirty-one cases, including our own, which had not been included in previous compilations.⁸⁻³⁴ The sum total of cases to date, therefore, seems to be 396, including Ludwig's 353, Mitra's four, Sloat and Peterson's eight and our thirty-one. However, from this grand total of cases we feel that at least one case should be subtracted, for reference to the original work cited showed that the condition was not present (Marta³⁵); therefore, the total number of cases is probably 395.

The term "simultaneous intrauterine and extrauterine" pregnancy as used herein refers to impregnation of the ectopic and uterine ova within a short time of each other. Faxon³⁶ expressed the belief that, of approximately 250 cases, 10 per cent represented an intrauterine pregnancy superimposed upon an ectopic pregnancy that had occurred one month to several years previously. The majority of these cases represented twin pregnancy with one ovum implanting ectopically and the other entopically.¹¹ The incidence of twins has been given as about 1.12 per cent of all births and fraternal-twin pregnancy occurs in about 75 per cent of cases of twins. Thus, the expected incidence of fraternal-twin pregnancy would be approximately 0.8 per cent of all pregnancies, and we can infer, then, that the expected incidence of simultaneous intrauterine and extrauterine pregnancy, calculated on this basis, would be about 0.8 per cent of all ectopic pregnancies, or 1 in 125. Martin and Meyer³⁷ gave the incidence one in 105. Furthermore, if the incidence of ectopic pregnancy is 0.37 per cent of all pregnancies and the incidence of simultaneous intrauterine and extrauterine pregnancy is 0.8 per cent of all ectopic pregnancies, then 0.37 per cent multiplied by 0.8 per cent gives a value of about

The blood pressure was 94 systolic and 64 diastolic, expressed in millimeters of mercury. A systolic murmur was heard over the entire precordium. Numerous râles were heard at the base of the left lung and vocal fremitus was decreased. The abdomen was distended and no peristaltic sounds could be heard. The upper part of the abdomen was slightly tender, the lower part was very tender bilaterally and the muscles were rigid. There was marked rebound tenderness of the lower part of the abdominal wall. Pelvic examination revealed that the cervix was large and softened. The uterus could not be outlined because of pain. Pain was elicited by moving the cervix and there was tenderness in both fornices.

A catheterized specimen of urine was taken. The specific gravity was 1.021 and the reaction was alkaline. There were occasional erythrocytes and leucocytes. The hemoglobin concentration was 11.6 Gm. per 100 c.c. of blood and the leucocyte count was 11,100 per c.mm. of blood. The differential leucocyte distribution was lymphocytes 18 per cent, monocytes 4 per cent, neutrophils 77 per cent and eosinophils 1 per cent. The sedimentation rate was 63 mm. in one hour. Cultures of material taken from the cervical and urethral ostia were negative for Neisserian organisms.

It was decided that the patient had an acute abdominal condition requiring surgical exploration, possibly a degenerating fibroid, and forty-eight hours from the time of admission she was operated on.

With the patient under nitrous oxide and ether anesthesia, a primary midline incision was made in the abdomen. Approximately 150 c.c. of blood in the abdomen had escaped from the fimbriated end of the the left Fallopian tube. This tube was the site of an unruptured ectopic pregnancy. The condition of the ovaries and the size of the uterus were not noted. Bilateral salpingectomy was done at the patient's request. Uterine retroversion and prolapse were corrected by a Gilliam type of suspension.

The pathologist's finding was chronic salpingitis in the right Fallopian tube and ectopic pregnancy in the left.

The patient was dismissed from the hospital on the tenth postoperative day. Five days later, at the time of dismissal from the clinic, the cervix was still soft and the uterus was anteverted.

Three months later the patient registered at the prenatal clinic. The size of the uterus was that of a four months' gestation. The result of a Friedman test was reported as positive. After an uneventful prenatal course, the patient delivered spontaneously a full-term male child.

CASE 2.—A 34-year-old white woman was first seen at her home on June 5, 1946, because of pain in the right lower quadrant. The pain had begun five days before she asked for help. It was mild at first but became severe and cramping. The patient had what was described as a scant menstruation for two days, which accompanied the pain. During the day on which she was seen, she had experienced severe right lower quadrant pain which extended down her thigh and forced her to stop working. The next day she was admitted to the hospital after having spent a quiet night, but before admission the same pain had recurred.

The patient stated that her menstrual periods had always been regular, but that she had had none for two months before admission to the hospital. She was gravida i, para 0. She had had pulmonary tuberculosis and her appendix had been removed eight years prior to admission.

The blood pressure was 125 systolic and 75 diastolic. The pulse rate was 96 per minute, and the temperature was 99.8° F. Pelvic examination revealed oozing of blood from the external cervical os and tenderness when the cervix was lifted. The adnexal regions were somewhat tender.

The specific gravity of the urine was 1.020 and the reaction was acid. There was grade 1 albuminuria (on the basis of 1 to 4 in which 1 represents the least and 4 the most severe condition) and a slight amount of reducing substances was present in the urine. The concentration of hemoglobin was 10.6 Gm. per 100 c.c. of blood and the leucocyte count was 8,600 per c.mm. Cultures taken from the cervix and urethra were negative for Neisseria gonorrhoeae. The result of the Friedman test was reported as positive.

six corresponding intrauterine pregnancies, in three the patient went to term,^{21, 25, 42} in the fourth the patient aborted in the first trimester¹⁴; in the fifth, the patient had an ectopic pregnancy and was operated on at seven and a half months' gestation and the twin fetuses died.³¹ The sixth patient was delivered of the intrauterine fetus by cesarean section when the birth canal was found to be obstructed by a seven months' mummified ectopic fetus.⁴⁸

The time elapsing from the last menstrual period to the onset of symptoms for which an operation was done varied from four to eighteen weeks in forty-eight patients, with an average of 8.7 weeks.

The rate of survival of the intrauterine fetuses was very satisfactory. In twenty-nine patients, the fetus in the uterus reached a viable age.^{1, 10, 11, 16-19, 21-25, 27-31, 33, 36, 39, 40, 42, 48, 49, 51, 55, 56} On the other hand, twenty-nine patients did not retain the intrauterine fetus;^{1, 3, 6, 7, 9, 11-14, 20, 26, 32, 34, 37, 38, 41, 44-47, 50, 52-54, 56, 58, 61, 62} however, in fourteen of these, the intrauterine pregnancy was disturbed before discovery of the ectopic pregnancy, either by spontaneous abortion, curettage, hysterectomy, or injury, as occurred in one case in which the fetus was killed when the mother was kicked by a horse^{1, 3, 7, 11-13, 21, 34, 45, 47, 52, 58}; the other fifteen patients lost the intrauterine fetus after discovery of the ectopic pregnancy. In eleven cases, the outcome of the intrauterine pregnancy could not be determined. The possible fetal survival rate after termination of the ectopic pregnancy was, therefore, twenty-nine out of forty-four (65.9 per cent).

The preoperative diagnosis was correctly made six times in sixty-nine cases.^{1, 11, 21, 32, 62} In these six cases, however, two patients first had had spontaneous abortions^{1, 11} and, in one, fetal death from external trauma occurred before the ectopic pregnancy was diagnosed.²¹ Correct preoperative diagnosis, therefore, occurred three times in sixty-nine cases (4.3 per cent). Even after the abdomen was opened, in sixty-three cases, the diagnosis of coexistent intrauterine pregnancy was made and recorded in only twenty cases.^{1, 6, 10, 11, 16, 20, 21, 29, 31, 36, 37, 39, 41, 44, 46, 48, 50, 53, 62} The relatively low incidence of accurate operative diagnosis is perhaps explained both by the infrequent occurrence of this condition and by the fact that enlargement of the uterus frequently occurs during an ectopic pregnancy. When ectopic pregnancy is found the surgeon is not likely to think of a coexisting intrauterine pregnancy.

As indicated above, six patients did not have sufficient symptoms for surgical exploration and, of these six, in four the ectopic fetuses reached term, in one it reached seven and one-half months' gestation, and in one a mummified ectopic fetus was found at seven months' gestation.

Report of Cases

CASE 1.—A 29-year-old white woman was admitted to the hospital complaining of generalized abdominal pain which had begun two weeks prior to admission. Three weeks before admission, at the time when a menstrual flow should have occurred, the patient had abdominal cramps and backache which lasted for three days and then ceased. No menstrual flow developed. During the succeeding week the patient had no complaints; then, two weeks before admission, low bilateral abdominal pain, which was worse on the left side, developed. The pain continued to become progressively more severe, and, at the time of admission, she had generalized abdominal pain. The patient had vomited from one to three times daily for two days. The last bowel movement had occurred two days prior to admission and the stool was black, but the patient had been taking some medicine for "gas," which she had passed freely until two days before being seen.

The patient had been treated for Neisserian infection in 1937. She had had two living children, followed by three spontaneous abortions which occurred at about three months' gestation. The last regular menstrual period was two and one-half months prior to admission.

TABLE VII

| PATHOLOGICAL REPORTS OF TISSUE EXAMINED | NUMBER |
|--|--------|
| Cervicitis | 251 |
| Fibrosis uteri or uterine vascular changes | 68 |
| Leiomyomas | 37 |
| Hyperplastic endometritis with polyps | 25 |
| Endometriosis | 8 |
| Fibroma of ovary | 3 |
| Carcinoma of cervix (early) | 3 |
| Carcinoma of fundus uteri | 1 |

cinoma of the cervix died three years after operation even after curative doses of radium and x-ray treatment had been carried out.

The anesthesia used was 270 spinals with the majority of these associated with Pentothal analgesia. The only disagreeable reaction from the anesthesia was in five cases of spinal anesthesia in which headache appeared, but all cases cleared up in five days with lowering of the head, sedation, and daily doses intramuscularly of nicotinic acid (100 mg.).

The follow-up results in this series from six months to ten years:

| | |
|--------------|-------------------------|
| Good: | 230 cases—76.6 per cent |
| Satisfactory | 45 cases—15.0 per cent |
| Poor: | 25 cases— 8.3 per cent |

Of the twenty-five patients having poor results, there were only six who had urgency incontinence. There were eight having slight recurrence of cystocele from two to five years after operation, most of them without symptoms. The remainder had subjective symptoms of backache, pelvic pain or fullness, and some dyspareunia, all referable to the pelvic structures. The average age of the patients with poor results was over 42 years; only two of the twenty-five patients were under 40 years of age.

The two patients with complications of pneumonia were over 44 years of age and the eight with recurrence of cystocele were over 40 years of age and had had long duration of symptoms.

Comment

It seems evident that the older the individual and the longer the duration of the pathology, the lower the chance of complete cure. Therefore, cystoceles and rectoceles and the associated pelvic pathology should be anatomically corrected soon after the completion of the family or about 40 years of age, so that the mother can be spared the long years of debilitating symptoms, and have more assurance of complete cure and be better able to assume properly her responsibilities of middle life.

Summary

1. An analysis of 300 cases of anterior and posterior colporrhaphy with associated pathology is presented.

2. From pelvic relaxation to complete prolapse, the process is essentially the same, varying only in degree.

3. Cystoceles and rectoceles are direct traumatic hernias and should be so considered and repaired, with the same meticulous anatomical care as hernias in other locations.

Over a period of five days, the patient continued to have mild, cramping, abdominal pain with some spotting of blood. She then experienced some pain in the region of the right shoulder and in the right adnexal region when examined bimanually. It was thought, after examination with the patient under anesthesia, that ectopic pregnancy existed on the right side, although no definite mass but only some thickening in the right adnexal region was noted.

At abdominal exploration, the lumen of the right Fallopian tube, at its middle portion, was found to be the site of an unruptured ectopic pregnancy and the tube was removed. About 100 c.c. of old, clotted blood was present in the pelvic cavity. The uterus was enlarged to a size consistent with that at two and one-half months' pregnancy and it was believed to be the site of another pregnancy.

One month later the patient was admitted to the prenatal clinic and an intrauterine pregnancy of three months' duration was present. After an uneventful prenatal course and after a labor in which the first stage lasted thirty-one hours and the second stage one hour, the patient was delivered of a full-term, living, female infant.

Discussion

The most significant point we encountered in our study of simultaneous intrauterine and extrauterine pregnancy was the drop in the maternal fatality rate from an over-all figure of 19 per cent to one of 1.4 per cent, which is compatible with a more modern concept of surgical risk. The lower rate is, of course, due to earlier diagnosis of the ectopic condition, earlier operation, and replacement of the blood and fluid loss. The replacement of blood promptly is the largest single recent factor in the reduction of fatality rates since everyone has agreed for years that the only treatment for ectopic pregnancies is early operation.

There was but one maternal death in the series since 1935, and, for this reason, we felt that the added complication of an intrauterine pregnancy did not appreciably increase the surgical risk. This death occurred after a two-day labor and cesarean section, at which a mummified fetus was found obstructing the birth canal. Death was attributed to a combination of maternal exhaustion, blood loss, and peritonitis.

The survival rate of the intrauterine fetuses is also of interest. Twenty-nine living children were delivered from the sixty-eight surviving patients. Since the outcome of the pregnancy is not mentioned in eleven cases and since, in fourteen, the intrauterine pregnancy was terminated before or at operation, the occurrence of twenty-nine live births out of a possible forty-three is remarkable.

The diagnosis was correctly made preoperatively six times in the group of sixty-nine cases, but in three, abortion of the intrauterine fetus before operation made the diagnosis easier. The diagnosis depends, of course, on evidence for an intrauterine, as well as an extrauterine, pregnancy. If a patient gives a history of a previous ectopic pregnancy, it is an added point for the possibility of a second one; chiefly, however, the history reveals the possibility of conception, as evidenced by a period of amenorrhea lasting a few days to several weeks, followed by a period of irregular spotting. If the spotting is due to an ectopic pregnancy the blood is often dark and viscous,

while the bleeding from an aborting intrantrine pregnancy is usually heavier and the blood is a brighter red. If there is an excess of vaginal bleeding plus signs of peritoneal irritation, a simultaneous intrauterine and extrauterine pregnancy can at least be suspected.

The indefinite signs of early pregnancy are most often conspicuous by their absence. Morning nausea, tingling of the breasts, increased pigmentation and cyanosis of the vaginal mucosa are helpful, if present. The cervix softens early and this sign is suggestive of pregnancy. Enlargement of the uterus occurs with either an ectopic or an intrauterine pregnancy and, if the enlargement is marked, then the possibility of coexisting intrauterine pregnancy should be suspected.

The presence of pelvic pain is very helpful. Such pain generally begins when internal bleeding starts. The overwhelming pain, with collapse, shock and so forth, of the complete rupture of a tube with massive intra-abdominal hemorrhage is not being stressed, as in these cases, the evidence that an intra-abdominal calamity has occurred is so apparent that the diagnosis should be made at once. The cases in which the condition starts as just a little intra-abdominal bleeding, the types of tubal abortion in which the products of conception are loosened but still in the tube, are the ones in which the possibility of diagnosis is offered before a catastrophe occurs. In this group, the pain is usually in one side or the other and is colicky at the beginning. This is followed by a dull, aching type of pain as a small amount of blood begins to collect in the peritoneal cavity. This blood, gravitating into the cul-de-sac, often causes painful defecation, which is a most helpful symptom.

The physical findings of a tender mass in one fornix and possibly a fullness and tenderness in the cul-de-sac are indicative of ectopic pregnancy.

However, even at operation, the diagnosis of simultaneous intrauterine and extrauterine pregnancy is not easy and in only twenty patients was it made by the surgeon. The enlargement that the uterus undergoes with ectopic pregnancy is sufficiently great that, unless the enlargement is marked, the surgeon closes the abdomen without suspecting the presence of the coexisting intrauterine fetus. A second sign that is excellent for double pregnancies, when it occurs, is the presence of two corpora lutea in the ovaries, indicating the possibility of two conceptions.

The treatment of these patients is that of any patient with an ectopic pregnancy, namely, early exploration. If an intrauterine pregnancy is also found, the patient can be given very definite hope of bearing a living child.

Summary and Conclusions

According to our study, the number of reported cases of simultaneous ectopic and intrauterine pregnancy, including our own, is approximately 395.

The maternal fatality rate in the cases encountered in the last eleven years compares favorably with that in cases of single ectopic pregnancy and, therefore, the added complication of the intrauterine pregnancy does not seem to increase the risk to the mother.

Of the sixty-nine patients referred to in the reports made in the last eleven years, twenty-nine were known to have delivered living children and only fifteen were known to have experienced termination of the intrauterine pregnancy after surgical treatment for the ectopic pregnancy.

Although we cannot often expect to make the diagnosis of double pregnancy in early cases, we should certainly be able, it seems, to make the diagnosis at the time of operation in more than twenty out of sixty-three cases.

In our two cases reported herein, the patients were delivered of normal full-term children several months after undergoing operation for ectopic pregnancy.

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HABITUAL ABORTION

A Pathologic Analysis of 100 Cases

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THE literature regarding habitual abortion is voluminous but comparatively few large series of cases have been reported. Moreover, most reports have dealt more with therapeutics than with pathogenesis. This study was undertaken, therefore, in the hope that a purely pathologic analysis of a comparatively large series of habitual abortions might afford valuable information for both the clinician and the pathologist. More particularly, it was desired to ascertain how often there was a common etiology in the successive abortions of a given patient.

Material

The material on which this study is based was collected from the pathologic records of the Boston Lying-in Hospital over a fifteen-year period (July, 1931, to July, 1946). The criteria used in selecting cases are as follows: Habitual abortion was considered to be a condition in which a woman has had two or more consecutive abortions before the twenty-eighth week of gestation. Each of these consecutive abortions must have been examined in the Boston Lying-in Pathology Laboratory, according to a standardized routine method of examination. Through the years, the method employed has been that first described by Mall and Meyer¹ with slight modifications, as discussed by Hertig and Edmonds.²

There was material from 123 patients which fulfilled these criteria. Further analysis revealed that, in twenty instances, either the history or the material submitted was inadequate for complete pathologic analysis. Three more cases were discarded because one of the two consecutive abortions in each case had been an ectopic pregnancy. There remain 100 patients with relatively complete clinical and pathologic records which form the basis of this study.

Results

The 100 patients selected according to the above criteria had a total of 220 abortions or 2.2 consecutive abortions per patient. There are 82 patients who have had two consecutive abortions, 16 who have had three, and 2 who have had four.

Habitual Aborters Without Common Etiology.—There are 42 patients in this group, representing 42 per cent of the series. Most of these patients had definite etiologies established for each of their abortions. There are, however, a small number of patients in whom a definite cause could not be ascribed for every abortion. In some of these abortions, the only pathology found was a grossly normal but macerated fetus. In others, a definite etiology could not be found because the material submitted from one abortion was insufficient for accurate diagnosis. The distribution of etiologies in this group was not statistically significant.

Habitual Aborters With Common Etiology.—There are 58 patients, or 58 per cent of the series, in this important group. The etiology for each specimen has been classified according to the method devised by Hertig and Livingstone² for their study of spontaneous abortions. Abortions with more than one possible etiologic factor have been classified according to the most significant pathology present. The distribution of repeated etiologies is shown in Table I.

TABLE I. NUMBER OF PATIENTS WITH HABITUAL ABORTIONS REPEATING THE SAME ETIOLOGY

| | TWO SPECIMENS | THREE SPECIMENS | FOUR SPECIMENS | TOTAL PER CENT |
|--|------------------|--------------------|-------------------|-------------------|
| <i>A. Ovular Factors</i> (43 cases) | | | | |
| 1. Pathologic ova | 33 | 3 | 0 | 36 |
| 2. Fetal anomalies | 1 | 1 | 0 | 2 |
| 3. Placental anomalies | 4 | 0 | 1 | 5 |
| <i>B. Maternal Factors</i> (15 cases) | | | | |
| 1. Uterine abnormalities | 7 | 1 | 0 | 8 |
| 2. Inflammatory conditions | 2 | 1 | 0 | 3 |
| 3. Miscellaneous | 2 | 2 | 0 | 4 |

Group A., Ovular Factors.—

1. *Pathologic ova:* The only departure in this group from the classical types of Mall and Meyer⁴ is the exclusion of grossly normal macerated fetuses without evident etiology for the abortion. The pathologic or "blighted" ovum constitutes by far the largest group with common etiology. Thirty-six patients, representing 36 per cent of the total series or 62 per cent of the habitual abortions with common etiology, had pathologic ova. Twenty-seven of these had various types, nine having the same type of pathologic ovum in each abortion.

Example (S-36-1187): Past obstetric history revealed one normal full-term delivery. Her second and third pregnancies each terminated in the abortion of a Group III hydatid mole (Hertig classification).⁴ This patient not only repeated a hydatidiform mole (a pathologic ovum in the strictest sense of the word) in both abortions but also presented the same type histologically in both cases.*

2. *Fetal Anomalies.*—Two of our 100 cases, or 3.45 per cent of the 58 patients repeating the same etiology, were apparently due to fetal anomalies.

Example (S-39-338): The first examined abortion of this 34-year-old para 0, gravida I revealed an anencephalic monster of twenty-six weeks' gestational age. Nineteen months later she aborted a second anencephalic monster of the same gestational age. Her third pregnancy nine months after this resulted in another anencephalic monster aborted at 9 weeks' gestational age.

3. *Placental Anomalies.*—This group involved 5 of our 100 cases, or 8.62 per cent of the 58 repeating the same etiology. Table II lists the types of placental anomaly found in the twelve abortions of these five patients.

It will be seen that premature separation is the most common type among these patients. The only patient repeating the same type of placental pathology in two consecutively examined abortions had premature separation. The other four patients had combinations of different types of placental anomalies. One of these, having four consecutively examined specimens, serves as an excellent example of this group.

*We also have the records from another hospital (not included in our series) of a patient who developed three moles consecutively.

TABLE II. TYPES OF PLACENTAL ANOMALY

| | |
|---|---|
| Premature separation of the placenta | 5 |
| Placenta circumvallata | 3 |
| Hypoplasia of the placenta | 2 |
| Placenta membranacea | 1 |
| Breus' mole (subchorionic tuberos hematoma) | 1 |

Example (S-36-579): Past obstetric history revealed a normal full-term delivery of her first pregnancy. A premature, seven months', otherwise uncomplicated delivery followed. Her next pregnancy resulted in the abortion of a normal fetus with a complete circumvallate placenta. Three succeeding pregnancies and abortions revealed in their respective order—a normal fetus accompanied by placenta circumvallata; a normal fetus with premature separation of the placenta and questionable low implantation; and lastly, a normal fetus in the presence of a complete circumvallate placenta.

Group B. Maternal Factors.—

1. *Uterine abnormalities:* This group constituted 8 per cent of the entire series and 13.8 per cent of the series repeating the same etiology. It is, therefore, second only to pathologic ova as a cause of habitual abortion among our patients. All of the fetuses and their placentas in this group were essentially normal. Furthermore, each of these patients repeated the same etiology in every abortion. These findings support the concept of uterine abnormality as a factor in habitual abortion.

The types of uterine abnormality found were retroversion, leiomyomas, low implantation of placenta including placenta previa, and abnormal fixation due to a previous Latzko section. This last abnormality was apparently responsible for three consecutive abortions of normal ova in one patient.

In analyzing the various types of uterine abnormalities, it might readily be said that each or all of the abortions due to these causes are theoretically salvageable and might have been saved, if each cause had been corrected. To prolong pregnancies involving low implantation until viability is reached might well be condemned. However, that prevention rather than treatment can be employed in some of these low implantations is well illustrated by one of the patients in our series. This particular patient had four abortions. The first two were recorded in her past obstetric history. The last two were consecutively examined, both revealing low implantation with premature separation. Following a uterine suspension for retroversion, she delivered a viable normal premature infant and a normal placenta. Whether this operative procedure prevented this particular pregnancy from aborting can only be surmised.

Low-implanted placentas are considered as a maternal or uterine factor rather than ovular or placental because of the relatively high incidence of placenta previa in multiparas. This suggests that low implantations are due to some abnormality of the multiparous uterus rather than of the ovum per se. The two patients in our series who had low implantation, were both gravida iii at the time of their first abortion.

The most common uterine abnormality was retroversion of the uterus, which was present in three of the eight patients.

Example (S-44-938): This 25-year-old, gravida I, had a spontaneous abortion the sixth week of her pregnancy. The fetus was normal. Nine months later she again aborted a normal fetus of twenty and one-half weeks' developmental age, according to its crown-rump length.⁵ A third-degree incarcerated retroversion of the uterus was found.

2. *Inflammatory conditions:* This maternal factor accounts for three cases in our series, or 5.17 per cent of the 58 patients repeating similar etiology.

It is second only to the fetal anomaly group of two patients in being the least common factor in the series.

Two of these patients had two consecutively examined abortuses, the third having had three. Each of these patients had a combination of infections in each consecutive specimen rather than repeating the same type of inflammation.

Sterile decidual necrosis and marginal types of placentitis are not included in this series. The former is now recognized as one of a triad, along with thrombosis and hemorrhage of the decidua, found in most spontaneous abortions, while the latter is consistent with ruptured membranes of any appreciable length of time.

None of these inflammatory involvements were believed to have originated outside of the uterus, the infection being confined in each case either to the endometrium (decidua) or the placenta, with or without subsequent fetal infection. In view of this observation, one might well conceive the possibility of an induced abortion. However, this concept hardly seems feasible in this group of patients, since these abortuses were sent to the laboratory as a diagnostic problem in the therapy of habitual abortion.

Example (S-35-1089): The patient was a 34-year-old, gravida i, whose first pregnancy terminated in an abortion. The pathologic examination revealed an anatomically normal ovum of 9 and 5/7 weeks' developmental age, whose associated decidua showed acute bacterial inflammation due to gram-positive cocci. Sixteen months later, a normal ovum aborted completely at twelve weeks, apparently due to acute bacterial inflammation of the decidua and adjacent placental tissue. Streptococci were demonstrated by Gram stain in these tissues.

3. *Miscellaneous:* This group includes four patients in our series with three different common etiologies for their abortions. Two had endometriosis, one toxemia of pregnancy, and one hypothyroidism. Three of the four patients each representing a different type of etiology, are given below.

Endometriosis (S-42-452): This 28-year-old, gravida i, aborted a normal fetus of thirteen plus weeks' developmental age in April, 1942. In June, 1942, a laparotomy revealed extensive endometriosis as well as a pseudomucinous cyst of the ovary. The uterus was not removed because of the patient's desire for another pregnancy. In February, 1943, she again aborted a normal fetus of eighteen weeks' developmental age.

Toxemia (S-44-407): The past obstetric history revealed that the first pregnancy resulted in a normal living premature infant, the second in a seven months' stillborn infant, and the third in normal, full-term delivery. Two subsequent pregnancies terminated in abortions, both of which (examined in our laboratory) revealed a normal twenty-six week fetus with extensive placental infarction. The mother had a toxemia with all five pregnancies.

Hypothyroidism (S-41-1172): The past obstetrics history revealed that her first pregnancy, at 17 years of age, resulted in a normal, full-term living infant. Five abortions followed, all of which terminated at ten weeks' gestational age. Following the last of these abortions, she was seen as a sterility problem, at which time hypothyroidism was diagnosed and thyroid therapy instituted. In spite of this, three more abortions ensued, all at ten weeks, each of which was examined in our laboratory. The sixth abortion, the first examined specimen, revealed a pathologic ovum, group 3-A.¹ (While only a ruptured chorionic sac was found, a fetus presumably had originally been present.) The patient's seventh abortion was a slightly macerated, otherwise normal fetus of approximately eight weeks' developmental age. Her eighth abortion was an extensively macerated, but normally developed fetus of similar age. The accompanying products of conception of each abortus

revealed only immature placental tissue with decidual thrombosis, necrosis, and hemorrhage. Thus, in spite of known hypothyroidism with thyroid therapy for three years, three essentially normal pregnancies aborted, each at approximately ten weeks' gestational age. It is noteworthy that all abortions occurred at this stage of pregnancy.

Discussion

Previously, 23 of the 123 patients in the initial series were excluded because of inadequate data. The omission of these 23 cases did not influence the statistical validity of this study. In the original series of 123 patients, 58.3 per cent of this number were found to repeat the same etiology. Following the exclusion of these patients, 58.0 per cent of the resultant 100 habitual aborters were found to repeat similar etiology, a variance of only 0.3 per cent.

Only 2 Rh-negative patients were present in the entire series and, in these 2 patients, other causative factors produced the repeated abortions. This finding is apparently in agreement with Hunt's⁶ contention that the Rh factor plays little or no part as a cause of habitual abortion. However, many of our cases occurred before the discovery of the Rh factor and, hence, our data are not really significant with respect to this point.

The results of this study closely parallel those of 1,000 spontaneous abortions analyzed by the same technique,³ thus affording an unusual opportunity for etiological and statistical comparison. Only those factors common to both series are included for comparison. The "miscellaneous" group is not a true comparison, because it includes different types of etiology in each study. It is included, however, merely for the sake of completeness. Table III presents a résumé of the etiology (repeated) in 100 habitual aborters versus the etiology (general) in 1,000 cases of spontaneous abortion.

Two interesting features are apparent from this comparison:

- (1) In both series, the percentages for any given factor are closely parallel.
- (2) In both series, all factors are in approximately the same proportion to one another.

The close relationship of these two series suggests that the etiological factor responsible for spontaneous abortion may also be responsible for habitual abortion.

If statistics are valid, and those involving this series have been found to be so,^{*} it becomes apparent that more than half of the 100 patients in our series, or 58 per cent, aborted repeatedly because of the same etiological factor.

TABLE III COMPARATIVE ETIOLOGY—HABITUAL VERSUS SPONTANEOUS ABORTIONS

| | 100 HABITUAL ABORTERS | PER CENT | 1,000 SPONTANEOUS ABORTERS | PER CENT |
|-----------------------------|--------------------------|-------------|-------------------------------|-------------|
| 1. <i>Ovular Factors:</i> | | | | |
| a. Pathologic ova | 36. | | 48.9 | |
| b. Fetal anomalies | 2. | | 3.2 | |
| c. Placental anomalies | 5. | | 9.6 | |
| | | 43. | | 61.7 |
| 2. <i>Maternal Factors:</i> | | | | |
| a. Uterine anomalies | 8. | | 6.4 | |
| b. Inflammatory conditions | 3. | | 2.0 | |
| c. Miscellaneous | 4. | | 1.2 | |
| | | 15. | | 9.6 |
| | | 58 | | 71.3 |

*The authors wish to express their appreciation to Miss Jane Worcester of the Harvard School of Public Health, Department of Biostatistics, for her review and analysis of all the material, including the statistics of this study. Her conclusion was that the statistical analysis of the material was significant and valid.

The significance of this finding becomes still more apparent if the statistics are more closely analyzed. A 58 per cent result in any series involving etiology would seem comparatively low compared to any other given series of cases. However, one should keep in mind that each of these 100 patients constitutes "a series within a series" in whom 2 or more abortions are involved and, when considered as such, the *collective* figure of 58 per cent repeating the same etiology is obviously quite significant. This figure might be still higher were it not for several patients in our series declared as not repeating similar causes simply because their abortuses could not be classified as to etiology.

In Table IV, the 58 patients repeating similar etiology are divided into three groups including those patients having two, three, and four consecutively examined specimens, respectively.

It is true that a division of our series into these three groups results in progressively smaller numbers for each, the statistical value in turn becoming only of relative importance. However, the definitely progressive rise in the incidence of repeated etiology in these three groups would seem to indicate that the more a patient aborts, the greater is her tendency to repeat the same etiology.

Summary and Conclusions

The etiology of all our large series of 100 habitual aborters varies both in extent and proportion, as does a series of 1,000 spontaneous abortions also studied in our laboratory. Individually, however, these habitual aborters repeated the same etiology in 58 per cent of the cases; 43 per cent being due to ovular factors and 15 per cent due to maternal factors. Pathologic ova were found to be the commonest etiology in habitual abortion, occurring in 62 per cent of the 58 cases. All other causes accounted for less than 10 per cent each of habitual abortions. Furthermore, the more often these patients aborted, the more often they repeated the same etiology.

TABLE IV. PROGRESSIVE INCREASE OF RECURRENT ABORTIONS AND THEIR REPEATED ETIOLOGY

| | | | |
|----|---|-----|------|
| 1. | Number of patients | | |
| | with 2 consecutively examined abortuses | 82. | |
| | Repeating same etiology in both specimens | 43. | |
| | Percentage repeating same etiology | | 52.4 |
| 2. | Number of patients | | |
| | with 3 consecutively examined abortuses | 16. | |
| | Repeating same etiology in all 3 specimens | 8. | |
| | Repeating same etiology in 2 of 3 specimens | 5. | |
| | Total repeating same etiology | 13. | |
| | Percentage repeating same etiology | | 81.2 |
| 3. | Number of patients | | |
| | with 4 consecutively examined abortuses | 2. | |
| | Repeating same etiology in all 4 specimens | 1. | |
| | Repeating same etiology in 2 of 4 specimens | 1. | |
| | Total repeating same etiology | 2. | |
| | Percentage repeating same etiology | | 100. |

The findings of our study would seem to warrant a revision of the approach to the clinical problems involved in habitual abortion. It should be evident that any woman who aborts is potentially an habitual aborter. Therefore, it is important that the very first abortus of any patient should be

4. The author's steps in the repair of these hernias are presented.
5. A plea is made for anatomical repair of the hernias as soon as the family is completed or when the patient is about 40 years of age.
6. Proper anatomical repair, at about 40 years of age, will prevent long years of disabling symptoms, give more satisfactory results, avoid complications, and enable the mother to have better health to assume her responsibilities in middle life.

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Discussion

DR. E. A. EDWARDS, Chicago.—Dr. Johnson presents a series of 300 patients operated upon for the cure of cystocele, rectocele, and associated uterine diseases. The indications for these procedures are substantiated by the symptoms complained of by these patients. He reviews the accepted operative techniques that are used in the repair of these lesions. He suggests an anatomical report of these lesions and makes a plea for their early correction at or before the age of 40.

Certainly we all agree that these patients need an anatomical repair; however, the advisability of their correction at the age of 40 needs some discussion. In this series presented today, 50 per cent of the women were under forty. Repair of these lesions in patients in the child-bearing age, unless adequate sterilization is assured, invites future surgical procedures. These secondary procedures are always much more difficult than the original operations. I believe these lesions should be repaired when symptoms are present and when the family is complete, but that sterilization should be part of the operative procedure.

Many of these lesions do not appear until the patient is sixty or seventy. Then, acutely, a prolapse of the uterus occurs. These extensive cases are more easily repaired than are the smaller lesions. The anatomical planes are more distinctly separable and a more exact anatomical correction is obtained.

It is interesting to observe that in this series, 119 women complained of abnormal bleeding, 112 of a leucorrheal discharge, 24 of postmenopausal bleeding, and 38 of dysmenorrhea in addition to the symptoms attributable to the laceration. We feel that the procedure of choice in patients who have had such symptoms is vaginal hysterectomy and repair. This removes the possibility of future pregnancies, obviates possible future removal of the uterus because of uterine pathology and, above all, corrects most adequately the symptoms complained of. Eighteen patients in this series had cervical amputations and ligations of the Fallopian tubes. We try to avoid cervical amputations unless the amputation is associated with the Manchester operation. Certainly the repair of cystocele, amputation of the cervix, and ligation of the Fallopian tubes is a more trying procedure than to do a vaginal hysterectomy and repair.

NECROPSY FINDINGS IN PATIENTS WITH CARCINOMA OF THE CERVIX

Implications for Treatment

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IT IS generally inferred that fatality from carcinoma of the cervix is not the result of overwhelming dissemination of the disease, but rather to disturbances secondary to the presence of an advanced neoplasm in the pelvis, i.e., uremia from occlusion of the ureters, infection, or hemorrhage, or a combination of these factors. A perusal of the literature fails to reveal many reports with clear-cut data on this question.

In Pearson's¹ study of 57 autopsies of patients dying of carcinoma of the cervix, the most striking postmortem finding was stricture of the ureters, occurring in 75 per cent. Either pyonephrosis or pyelonephritis was present in 22 per cent. Uremic deaths occurred in 25 per cent. Peritonitis accounted for 19 per cent of the deaths. Distant metastases were present in only 25 per cent of the series.

DeAlvarez,² in summarizing the causes of death in 55 patients who died of carcinoma of the cervix, found the incidence to be ureteral obstruction in 40 per cent of the series; pulmonary causes in 31 per cent; and gastrointestinal causes in 13 per cent of the cases studied.

A review of the autopsy records in the Memorial Hospital from 1917 to the present, 1948, a period of thirty-one years, has shown protocols in 65 patients who died of cervical cancer. At first glance this would not appear to be a very large number, especially from a hospital devoted practically completely to neoplastic diseases. Furthermore, a low general autopsy incidence in the hospital would further contribute to the existence of such a small series. On the other hand, the inference is rather clear that cervical cancer is relatively slowly growing, and therefore an institution which could not serve as a center for terminal care would not be expected to have records in its autopsy files of patients whose final stages of disease were of relatively slow evolution—as seems to be the case in carcinoma of the cervix.

Presence of disease beyond the pelvis at time of death: Among the 65 necropsies, thirty-two presented macroscopic spread of disease beyond the pelvis. Of the latter, twenty-four had metastases to the periaortic nodes. In 9 per cent of these, the metastases appeared confined to these nodes, in the remainder there were also metastases elsewhere. The sites were: lungs and mediastinum, eleven; liver, six; cervical lymph nodes, three; miscellaneous foci including left adrenal gland, peritoneum, serosa of bowel, spleen, thoracic wall, peripancreatic nodes, subcutaneous tissue, and kidney. In six instances metastases were not described in the periaortic nodes.

thoroughly examined pathologically. This is apparently not often done, since many of the hundreds of records we have reviewed revealed previous abortions which had not been submitted for examination. The fact that, in our series, 99 per cent of habitual aborters returned repeatedly to the same clinic or physician demonstrates the feasibility of having all abortions examined pathologically as an aid to prognosis and therapy. By submitting all abortions to such examination, both the patient and her physician can become intelligently prepared for any subsequent abortions.

An increasing number of reports in the literature have appeared showing the satisfactory results from using specific therapy against certain factors causing recurrent abortions; for instance, the use of endoerines in apparently forestalling the production of pathologic ova and vitamin E in preventing fetal anomalies. To give these treatments more rationale, the physician should know, whenever possible, whether the previous accidents of pregnancy were due to definite ovular or maternal causes. An appeal for this approach, pointing out the means of obtaining it, is the essence of this study.

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The factor of infection was an important one. General peritonitis, pelvic peritonitis, pelvic abscess and septicemia in varying degrees of combination were the immediate assignable causes of death in 24 patients, 38 per cent of the series. These were secondary to a recent operation, to a pelvic abscess complicating pelvic neoplasm, or secondary to necrosis of pelvic tissues from irradiation. The data are summarized in Table I.

TABLE I. SUMMARY OF DATA PRESENTED IN TEXT

| | |
|---|-----------------|
| Total number of necropsies, patients dying with primary diagnosis of carcinoma of the cervix | 65 (100%) |
| Total number of patients presenting no gross evidence of spread beyond the pelvis at necropsy | 33 (50% Plus) |
| Total number of patients presenting metastatic carcinoma beyond the pelvis at necropsy | 32 (50% Minus) |
| Total number of patients with periaortic metastases as well as metastases elsewhere | 24 (38.4%) |
| Total number of patients with periaortic metastases only | 9 (13.8%) |
| Other sites of metastases: | |
| Lungs and/or mediastinal nodes | 11 (18.4%) |
| Liver | 6 (9.2%) |
| Cervical lymph nodes | 3 (4.6%) |
| Extra-pelvic metastases in patients without periaortic nodes involved | 6 (9.2%) |
| Number of patients found to have no residual neoplasm anywhere | 5 (7.7%) |
| <i>Assigned causes of death</i> | |
| Cases without extrapelvic spread | |
| Peritonitis | 10 (15.5%) |
| Pelvic abscess | 5 (12.2%) |
| Septicemia | 2 (3.1%) |
| Uremia | 6 (9.3%) |
| Cases with extrapelvic spread | |
| Uremia or pyonephritis | 12 (18.4%) |
| Peritonitis | 6 (9.3%) |
| Septicemia | 4 (6.2%) |
| Intestinal obstruction | 2 (3.1%) |
| Uremia and/or pyonephritis—whole series | 18 (27.7%) |
| Peritonitis and/or pelvic abscess—whole series | 18 (27.7%) |
| Pelvic abscess and/or septicemia—whole series | 6 (9.3%) |
| Cases with constriction of ureters (Those with and without fatal uremia) | 41 (63%) |

Summary

In a review of 65 necropsies of patients who had carcinoma of the cervix, the following salient features appear deserving of emphasis:

1. Cancer of the cervix tends to spread primarily via the lymphatics, the periaortic nodes being first involved outside the pelvis in most instances.

2. Half of the patients died from various causes other than wide dissemination of the disease since necropsy revealed no gross evidence of neoplasm outside the pelvis in this group.

3. Uremia was the immediate cause of death in 27.7 per cent of the series, and ureteral obstruction of varying degrees was present in 63 per cent of the cases.

The assigned causes of death were: uremia or pyonephritis, twelve cases; peritonitis, six; septicemia, four; tuberculous bronchopneumonia, one; empyema, one; intestinal obstruction, two; cause not stated, six.

Death without metastases beyond the pelvis: In the thirty-three subjects where macroscopically there were no metastases beyond the pelvis, death was ascribed to the following causes: peritonitis, ten; pelvic abscess, five; septicemia, two; pneumonia, two; septie pulmonary infarct, one; pulmonary embolus, one; pulmonary tuberculosis, one; pulmonary edema, one; uremia, six; hemorrhage into large bowel, one; pernicious anemia, one; cause not apparent, two.

Disturbances of the urinary tract: In forty-one of the sixty-five patients, irrespective of the presence of metastases beyond the pelvis, necropsy revealed some degree of ureteral obstruction with concomitant hydronephrosis. This would appear to be a part of the natural sequellae of uncontrolled cancer of the cervix, and as the latter continues to develop, the importance of the involvement of the ureters becomes progressively more significant, as regards the continued survival of the patient.

Extent of cervical carcinoma at time of death: Practically all of the patients in this series received irradiation therapy. Fifty-two presented residual or recurrent neoplasm in the cervix with or without pelvic or extrapelvic extension at the time of death. In six subjects there was no residual neoplasm in the cervix, but metastases beyond the pelvis were present. In five subjects there was no residual neoplasm in the cervix nor metastases macroscopically visible elsewhere. Death was due, among other things, to cirrhosis, one case, and extensive irradiation necrosis of pelvic tissues in five instances. No assignable cause for death was given in one case.

Discussion

The above data indicate that carcinoma of the cervix spreads beyond the pelvis primarily by lymphogenous metastases, the first extension being the peri-aortic lymph nodes. Following this a rather wide range of dissemination is manifested, as evidenced by the various localities of metastases, i.e., adrenals, spleen, liver, lungs, mediastinum, kidneys, etc.

As to treatment, the importance of some type of attack upon the lymphatic channels leading away from the cervix and out of the pelvis is strongly emphasized. The problem of purely local destruction of the primary growth is not much greater than the problem of blockage of the lymphatic pathways by which dissemination occurs. Irradiation therapy, it would appear, has limitations in this respect. Whether a systematic "en bloc" resection of the pelvic areolar tissue with lymph nodes and channels together with a panhysterectomy would yield improved results in the treatment of cervical cancer remains to be demonstrated, although theoretically, it is worthy of trial, inasmuch as a systematic surgical attack upon cervical cancer has not been carried out in recent years.

An important feature in the situation is the preservation of urinary tract function for as long as possible, since the data presented above, as well as in similar studies reported by others, reveals that a high incidence of immediate fatality is due to uremia caused by ureteral obstruction in the pelvis by the neoplasm. In the series reported above, 41 or 63% of the cases exhibited an appreciable degree of ureteral obstruction.

CYSTOSCOPY AND PYELOGRAPHY FOLLOWING PARAVESICAL EXTRAPERITONEAL CESAREAN SECTION

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THIS is a preliminary report of cystoseopic examination on a small number of cases (eighteen) following extraperitoneal section. The use of the extraperitoneal section has varied in its popularity, and for the most part over the years has been tried and then abandoned. Some surgeons have been expert in performing the operation, have no complaints to offer, and utilize the procedure frequently. Others have tried to perfect themselves in this technique, and, having encountered some difficulty, have become discouraged, and reverted to other means of delivery in the potentially infected or the frankly infected individual. Others have been deterred from attempting the operation because of objections raised against its use. A few of these objections are: (1) sharp dissection of the perivesical fascia lends to bladder and peritoneal perforation; (2) the bladder is markedly stripped of its fascia and nerve supply and that deformities and dysfunctions result therefrom; (3) there is too much handling of tissue and that the whole procedure is traumatic; (4) inability to be certain that the bladder has been removed from the lower uterine segment before incision of the uterus; (5) the removal of the bladder from the lower uterine segment so displaces the course of the ureters that ureteral injury may result by inadvertent incision of these structures; (6) the availability of sufficient room for the delivery of a large baby is markedly compromised; (7) the operation is too difficult and takes too long in the hands of the nonexpert. However, there are valid objections to the alternate choices used in the management of these cases.

Crainiotomy is not without hazard, and bladder injuries with persistent fistulae may result, not to mention the serious damage to the soft parts when done by inexperienced hands. Porro section is a terrific price for the young primiparous individual to pay who wants a child. Many have claimed "excellent" results by doing a transperitoneal cesarean section and depending on all the sulfonamides and antibiotics available to stop or limit the spread of infection in the potentially or actually infected case. Such a series has not been reported, and it is our contention that if enough of cases are handled in this fashion there will be many that will not respond to the sulfonamides and antibiotics and that there will be an increase in the maternal morbidity and mortality.

We have at our command not a new type of extraperitoneal cesarean section, but a modification of the old Latzko type as described by Norton.¹

4. Infection, principally as peritonitis, pelvic abscess, and septicemia in varying combinations appeared to be the immediate cause of death in 38 per cent of the series. Thus uremia and infection together were the immediate causes of death in 66 per cent of the series, not widespread malignant disease.

5. Aside from eradication or restraint of the neoplasm, preservation of urinary tract function and avoidance of infection appear to be the principal problems to be dealt with for the prolongation of life in patients with cancer of the cervix.

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temperature elevations intra partum. A uterine culture was taken at operation in all cases and was positive for staphylococcus aureus, albus or streptococcus anhemolyticus in nine cases. There were seven cultures that showed no growth at the end of three days and two were not reported. The average baby weight was 3,200 grams. The one bladder puncture that we have had in the last 250 cases was seen in this group. This injury was done by one of the resident staff.

Each patient was questioned carefully on bladder symptoms:—frequency, urgency, incontinence with or without stress or strain. Two patients had frequency, one had urgency, one had incontinence with stress, and one had incontinence without stress (patient with the bladder injury). This patient with the bladder rupture will be discussed separately. On cystoscopic examination the bladder was filled with 300 c.c. of fluid to test its filling power. Each patient permitted that amount of bladder distention, but complained of fullness and urgency. Examination of the bladder wall showed a normal mucous membrane with no cystitis, the ureteral orifices were clearly visualized and each ureter was catheterized. The trigone in a few instances showed some hyperemia and various degrees of trigonitis. Cultures were taken from each kidney and all but two had sterile cultures. Each bladder seemed to have a normal contour on visualizing the interior. Intravenous or retrograde pyelography was carried out on each patient, and each has been reported as having a normal bladder shadow, normal ureters both in size and anatomic relationships, and normal kidney pelvises. The average time for dye excretion from each kidney was 3.3 minutes.

The patient with the bladder injury had been previously delivered vaginally after a prolonged labor of a living child, face presentation, weighing 3,200 grams. During this gestation she was admitted with a brow posterior, dipping into the pelvic inlet. At a sterile vaginal examination there was an attempted but unsuccessful conversion. The position now was an occiput transverse still in deflection attitude. After twenty-five hours of ruptured membranes and fifty-seven hours of desultory labor, the vertex was unengaged and the patient was morbid (temperature 102° F.). Under cyclopropane anesthesia, an extraperitoneal cesarean section was done. During the procedure the bladder was pierced by a finger, and this was due to the fact that the bladder was being removed from the lower uterine segment while it was still full. One must take time to empty the bladder if this accident is to be avoided. The bladder was repaired and postoperatively an indwelling catheter was left in place and continuous bladder drainage was maintained. The catheter was prematurely and mistakenly removed at the end of four days. On discharge from the hospital, it was noted that the patient had a vesicovaginal fistula. On her return three months later the fistula was still present. This could be seen on vaginal examination and was situated high on the anterior vaginal wall in the anterior fornix. Cystoscopic examination at this time showed a marked cystitis with a severe bullous edema of the mucosa. There was a hyperemia of the bladder interior especially in the region of the trigone. There was a traction diverticulum at the upper left-hand corner of the bladder at the site of the injury, and there was marked hypertrophy of the rugae. It was impossible to locate the ureteral orifices due to the edema present. At five months post partum the patient was again seen, and the fistula had completely healed spontaneously.

Conclusions

1. The series is not of sufficient number to make too dogmatic statements, but it can be said that in the uncomplicated case where bladder injury does not occur, there is no impairment of bladder function, and no disturbance of bladder or ureteral anatomy.

His description has given us a better understanding of the pelvic fascia or areolar tissues, as some now prefer to call this tissue. In answer to the aforementioned objections he has done away with (1) sharp dissection of the perivesical fascia, instituting blunt finger dissection and minimizing bladder and peritoneal puncture. These accidents may still occur, but is the "hurried" and inexpertly "quick" hand that gets into trouble. The bladder (2) is not completely stripped of its fascia but it is freed especially at the upper left-hand corner and made mobile. Norton has suggested the term "chicken yellow fat" for the fat pad that is lateral to and common to all bladders, and he has pointed out that in this fatty area the perivesical fascia is weak and may be picked up with the fingers and bluntly stripped away from the anterior surface of the bladder. This fat has been mentioned by others, but it has never been stressed as a landmark for the initial step in the dissection of the bladder. The entire procedure of stripping the bladder anteriorly (3) requires but one and at most two manipulations. The next step requires the removal of the bladder from the lower uterine segment. This must be done with the bladder empty and a gauze pad protecting the bladder. This organ is pulled down to the symphysis and slightly to the right. The bladder with its base, which is still attached to the lower uterine segment, is again protected by a gauze pad held in place by a retractor before any incision in the uterus is made. (4) If there is any doubt at this point that the bladder is not completely removed from the lower uterine segment, then it is refilled with fluid and landmarks re-established. The posterior peritoneal fold must definitely be identified and once it is, it is pulled up over the lower uterine segment using the periuterine fascia as a buffer. Norton advocates the use of a midline vertical uterine incision. If the incision is in the lateral portion of the lower uterine segment, the operator has not completely brought the bladder down and out of the way and the procedure is not being done correctly. (5) The uterine incision must be in the midline, thus it is not in proximity with either ureter, and the bladder base is amply protected with gauze pad and retractor. It is understood that the incision is made under direct vision and that blood and amniotic fluid must not obscure the operative field. (6) Sufficient room is obtained in the lower uterine segment by adequate elevation of the posterior peritoneal fold. (7) The average operating time for both attending and resident staff is forty minutes from skin to skin and ten minutes from skin incision to the delivery of the infant. The shortest elapsed time from skin incision to delivery of the infant in our hands has been just short of five minutes.

Since this operation is chiefly one of bladder dissection, it was thought necessary to test bladder function post partum. These patients were asked to return at about three months post partum for cystoscopic examination and for either intravenous or retrograde pyelography. The group consisted of fourteen private and 4 clinic patients, of which fourteen were primigravida and four were multigravida. The average length of labor was 33.4 hours and the average duration of ruptured membranes was 32.1 hours. Seven patients had

THE BACTERIOLOGY OF FALLOPIAN TUBES REMOVED AT OPERATION

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THIS investigation comprises a study of 72 patients from the wards and private service of the Women's Clinic of the Johns Hopkins Hospital. Seven patients had had a previous history of gonorrheal infection, 40 had doubtful histories and 25 had negative histories.

In 1921 Curtis isolated the gonococcus from Fallopian tubes removed at operation in 38 of 192 cases, but gross and microscopically these tubes presented a picture of acute inflammation. Curtis also isolated *Escherichia coli*, streptococci, and anaerobic streptococci from cases of salpingitis and perisalpingitis. Cordua and Keek in 1926, reported isolating paratyphoid B bacillus from an ovarian abscess. In 1931 Worral reported having isolated Staphylococci from infected Fallopian tubes. Caussade and Giullemin, 1934, isolated the colon bacillus from the tubes of a 12-year-old girl. Brown, 1835, isolated *Salmonella newport* from a case of bilateral pyosalpinx. Studdiford, Casper, and Seadron, in 1938, reported isolating gonococci from the tubes of 16 of 24 cases studied. The organisms were isolated by culturing pieces of tissue and exudate, never from pus, and occasionally were degenerate in form but rapidly assumed the usual characteristics upon subculture. Thirteen of the specimens yielding gonococci showed pathologic evidence of subacute inflammation, two were acute exacerbations of chronic salpingitis, and one showed evidence of chronic or healed salpingitis with marked structural changes in the walls of the tube. According to Cornell, until 1934 there were 71 published cases of actinomyces of the internal female genitals. American literature reported seven cases, English literature six, and the remainder were in other languages. Since then cases have been reported by Gardiner and Welsh, 1935; Côte and Tudhope, 1936; De Faria and Fiablo, 1937; Auster, 1940; and Ahumada and Chevalier, 1943.

Technique

Immediately upon removal at operation the tubes were placed in sterile Petri dishes and brought to the laboratory. If pus or fluid was present in the tubes or abscesses a small area was seared with a searing iron, a sterile glass capillary pipette inserted, and the material aspirated for cultural study. Pieces of tissue were thoroughly ground in sterile sand and 3.0 c.c. of pancreatic digest broth, pH 7.2, for buried foci of infection. All specimens were cultured in the following manner: A tube of Brewer's sodium thioglycollate medium was inoculated and incubated at 37° C. for seventy-two hours. Smears were made every twenty-four hours and examined microscopically. Aerobic and anaerobic streak plates were made on pancreatic digest blood (rabbit) agar, the former incubated for seventy-two hours and examined every twenty-four hours and the latter incubated for forty-eight hours and then examined. For isolation of the gonococcus streak plates were made upon pancreatic digest chocolate blood (human) agar and incubated in an atmosphere of approximately 10 per cent carbon dioxide for forty-eight hours. This medium was used because it had been previously shown to be most satisfactory for the isolation of the gonococcus from cervical cultures, Koch, 1946. Direct

2. With bladder injury, continuous drainage must be instituted and maintained until there is complete healing.

3. There have been no atonic bladders immediately postoperative or when seen at three months post partum.

4. Bladder manipulation is carried out on the empty bladder to avoid accidental puncture.

5. Uterine incision is in the midline and under direct vision so that even an anomalous or displaced ureter is not in the operative field.

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A curettage should precede all vaginal operations. Such pathologic lesions as carcinoma of the endometrium and cervix can be diagnosed by this preliminary curettage and investigation and the proper procedure can be instituted.

It should be noted that only three persons in this series had thrombophlebitis. In our fairly large series of vaginal hysterectomy, thrombophlebitis is most unusual and pulmonary embolus has not occurred.

I believe that ten cases of perineal infection in 300 cases is too high an incidence. However, the low incidence of urinary tract infections is exceptional. I would like to ask the author about his management of the postoperative urinary bladder.

It is our policy to correct the lesions as described in this series either by vaginal hysterectomy and repair or by the Manchester operation.

DR. W. O. JOHNSON (Closing).—I wish to thank Dr. Edwards for his frank discussion.

The repairs described are called radical because they entail a complete dissection of the involved parts, a replacement of the organs or structures into their normal positions, and a repair along anatomical lines; complying with the accepted principles of hernial repair of high imbrication of the sac and fascial approximation of the supporting structures.

The cystoceles and rectoceles are direct traumatic herniae, and should be repaired as hernia are repaired. Unless fascial planes are approximated and sutured, the herniae cannot be expected to hold. This procedure is applicable in the young as well as the old and should be carried out before irrecoverable changes occur.

In this series, there were eighteen patients under 30 years of age, where cauterization of the cervix, anterior and posterior colporrhaphy and the Fothergill advancement type of operation were employed. In five of these cases there was a subsequent pregnancy without complications at delivery. Only episiotomies were employed in the deliveries and these patients did not have subsequent pelvic floor relaxations.

In the group of women around 35 years of age, who had completed their family even beyond their financial capacity, an amputation of the cervix, together with vaginal sterilization, and anterior and posterior colporrhaphy was done. Such procedures have restored these women to useful heads of households without premature ovarian failure. There is a relationship between the endometrium and the prolongation of the proper ovarian function, and the above procedures serve both purposes in this group of cases.

The remainder of the cases with cervical amputation were in elderly women with normal uteri for their age, and in every case the uterine cavity was thoroughly curetted to rule out possible pathology. The uteri were left in place to aid in better support, less operative manipulation and risk, and a reduction in morbidity.

We do not advocate a vaginal hysterectomy unless the patient is over 37 years of age, or has intrinsic uterine pathology, fibroids, circulatory changes, etc., which indicates removal of the uterus. An endeavor is always made to suit the indicated operative procedures to the individual case.

Dr. Edwards asked about the postoperative care of the bladder. The postoperative treatment of the bladder in these cases is of greatest importance. The retention catheter which is placed in the bladder at the time of operation is retained for about four days. Continuous drainage is maintained and the bladder irrigated with warm, boric solution daily; once daily 30 c.c. of 5 per cent Argyrol solution is instilled into the bladder. After the fourth day, the catheter is removed and the patient tries to void. If she is unable to void as much as 150 c.c. at a time, a small simple catheter is placed in the bladder in the evening and allowed to drain. This permits rest and reduces bladder edema. In the morning the catheter is removed, and the patient tries to void, and this procedure is repeated until the patient is

smears were made of all pus, exudate, and ground tissues, stained by Burke's modification of the Gram stain and examined microscopically. For final identification all organisms were thoroughly studied according to their biochemical reactions. A gonococcus complement fixation test was made upon each patient.

Results

For convenience the patients in this study were grouped first according to the gross pathology of the Fallopian tubes (Table I) and second according to the histologic evidence of inflammation (Table II).

TABLE I. ORGANISMS ISOLATED FROM FALLOPIAN TUBES. ANALYSIS BASED UPON GROSS PATHOLOGY OF THE TUBES

| TYPES OF CASES | TOTAL NO. | CULTURE STERILE | GROWTH | | | | | | | |
|-------------------------------------|-----------|-----------------|--------------------|------------------------|-----------------------|--------------|------------|-------------------|----------------|--------------|
| | | | ALPHA STREPTOCOCCI | ANAEROBIC STREPTOCOCCI | HEMOLY. STAPH. AUREUS | STAPH. ALBUS | ESCH. COLI | ACTINOMYCES MURIS | MIXED CULTURES | UNIDENTIFIED |
| Tubes enlarged, fimbria occluded | 24 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tubes atrophic, fimbria occluded | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ovarian involvement, tubes occluded | 18 | 14 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 |
| Ovarian involvement, tubes patent | 7 | 4 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 |
| Lumen and fimbria patent | 22 | 19 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Totals | 72 | 62 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 1 |

1. Twenty-four showed enlargement of the tubes with fimbria occluded. All cultures were sterile.
2. One showed atrophy of the tubes with fimbria occluded. Cultures were sterile.
3. Eighteen showed ovarian involvement with tubes occluded. Fourteen of these had sterile cultures, four yielded growth, one an anaerobic streptococcus, one hemolytic *Staphylococcus aureus*, one *Actinomyces muris* and the other a mixed culture of *Clostridium perfringens* and diphtheroids.
4. Seven showed ovarian involvement with tubes patent. Four yielded sterile cultures and three yielded growth, one hemolytic *Staphylococcus aureus*, one *Escherichia coli*, and one an unidentified very small Gram negative rod growing only in the presence of blood.
5. Twenty-two showed the lumen and fimbria to be patent. Nineteen had sterile cultures and three yielded growth, one *Streptococcus salivarius*, one hemolytic *Staphylococcus aureus*, and one *Staphylococcus albus*.

TABLE II. ORGANISMS ISOLATED FROM FALLOPIAN TUBES. ANALYSIS BASED UPON HISTOLOGIC EVIDENCE OF INFLAMMATION

| TYPES OF CASES | TOTAL NO. | CULTURES STERILE | GROWTH | | | | | | | |
|-----------------------------|-----------|------------------|--------------------|------------------------|-----------------------|--------------|------------|-------------------|----------------|--------------|
| | | | ALPHA STREPTOCOCCI | ANAEROBIC STREPTOCOCCI | HEMOLY. STAPH. AUREUS | STAPH. ALBUS | ESCH. COLI | ACTINOMYCES MURIS | MIXED CULTURES | UNIDENTIFIED |
| No evidence of inflammation | 20 | 19 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Subacute inflammation | 31 | 26 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 |
| Chronic inflammation | 21 | 17 | 0 | 1 | 2 | 0 | 0 | 1 | 0 | 0 |
| Totals | 72 | 62 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 1 |

1. Twenty showed no evidence of an inflammatory process. Nineteen cultures were sterile and one yielded a growth of *Staphylococcus albus*.

2. Thirty-one showed evidence of subacute inflammation. Twenty-six yielded sterile cultures and five showed growth; one *Streptococcus salivarius*, one hemolytic *Staphylococcus aureus*, one *Escherichia coli*, one a mixed culture of *Clostridium perfringens* and diphtheroids and one an unidentified very small Gram negative rod growing only in the presence of blood.

3. Twenty-one showed evidence of chronic inflammation. Seventeen yielded sterile cultures and four showed growth: one an anaerobic streptococcus, two hemolytic *Staphylococcus aureus*, and one *Actinomyces muris*.

Discussion

Pus producing organisms other than the gonococcus were isolated in 13.8 per cent or ten cases of the 72 patients studied; from 16.1 per cent of the tubes showing histologic evidence of subacute inflammation, and from 19.0 per cent of the tubes showing histologic evidence of chronic inflammation. That the gonococcus was not isolated was not surprising, since it is a known fact that the organism soon disappears from the tubal mucosa, and the Fallopian tubes studied in this survey showed no evidence of acute inflammation.

The four strains of hemolytic *Staphylococcus aureus* isolated, three from tubes and one from the pus aspirated from bilateral ovarian abscesses, were probably toxin producing strains, since all produced beta hemolysis on blood agar plates, fermented mannitol, liquefied gelatin, and were coagulase positive.

The patient yielding the Gram-negative unidentified rod from tubal cultures yielded *Hemophilus influenzae* from cultures of the pus from bilateral ovarian abscesses. Brucella agglutination tests were negative.

Two patients had positive gonococcus complement fixation tests. One patient had a recent history of gonorrhea; the other denied ever having been infected.

Conclusions

1. In this study it was not possible to isolate the gonococcus from Fallopian tubes showing histologic evidence of subacute and chronic inflammation.

2. The Fallopian tube is not the focus of chronic gonorrheal infection.

3. The gonococcus is short lived in the tubal mucosa and apparently produces a low level of demonstrable antibodies, since only one patient in the series of seven having histories of a previous gonorrheal infection, and one patient in the 40 having doubtful histories had positive gonococcus complement fixation tests.

4. To my knowledge no other case has been reported in the literature of the isolation of *Actinomyces muris* (sometimes called *Streptobacillus moniliformis* and *Haverhillia multiformis*) from bilateral tubo-ovarian abscesses or of the isolation of *Hemophilus influenzae* from bilateral ovarian abscesses. If such cases have been reported, I have not been able to find them.

The author wishes to acknowledge the valuable assistance of Dr. J. Howard Brown and Dr. Richard W. Te Linde during this course of investigation.

Reports on the gross and histologic pathology of the specimens studied were obtained from the Pathology Laboratory of the Department of Gynecology.

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PYELOURETERAL DILATATION OF PREGNANCY AFTER DEATH OF THE FETUS

An Experimental Study

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EXPERIMENTALLY it has been shown that the fetus can be absent for months, or even the greater half of the normal length of gestation, without interrupting the physiologic state of pregnancy.¹ The fetus alone was removed, while the placenta was allowed to remain functional in the uterus, and when this was done in the latter half of pregnancy after the "hydroureter of pregnancy" had been established, the dilatation was seen to persist and even to progress, although the weight of the uterine contents had been diminished far below that which was attained before ureteral dilatation appeared.^{2, 3} Weight of the uterus with its contents was even further disqualified as the primary cause of ureteral changes in pregnancy; for, when the fetus was removed at an earlier stage before obvious distention of the ureter had occurred, it was found that the hydroureter could *arise and be maintained*. The placenta under these experimental conditions was spontaneously expelled at a time compatible with the birth of a viable infant. Therefore, it appears that the normal duration of pregnancy as well as its characteristic hormonal levels⁴ and the onset of contractions associated with the expulsion of uterine contents at term, are independent of the presence of the fetus. This experimental work was carried out in the rhesus monkey (*Macaca mulatta*), a primate with a twenty-eight day menstrual cycle and whose genital tract and reproductive physiology are strikingly like that of man.

After the study of several hundred pregnancies in the monkey, we now have three instances in which there was spontaneous death of the fetus from some inherent cause while the placenta remained hormonally active in relation to the mother organism. Thus, the essential factors of the earlier experimental work were duplicated. Pregnancy in the rhesus monkey lasts about six months, and the first evidence of a fetal skeleton is seen around seventy days. It is routine to make x-ray films of all pregnant animals at this time with added films before or later, according to the problem under consideration. The progress of pregnancy before the appearance of the fetal skeleton is followed by rectal palpation of the enlarging uterus and by x-ray films after intravenous injection of an opaque medium* which, when excreted by the pregnant animal, gives good visualization of the hilus and full length of the ureter in most cases. In the nonpregnant animal the contrasting medium passes through

*Diodrast was generously supplied by the Winthrop Chemical Company, Inc.

to the bladder so quickly that traces alone can be seen in the ureters. Only after the establishment of the definitive placenta about the thirty-fifth day,⁵ do the ureters fall under the hormonal influence exercised by that organ upon all smooth muscle. A slowing up of the urinary flow is a sign of pregnancy.

Monkey A.—Jan. 18, 1940, was the conception date initiating this pregnancy, first recognized on rectal palpation February 17. This was the second gestation for the animal born in the laboratory in 1935. The routine urogram on the seventy-sixth day of pregnancy showed an enlarging uterus but no skeleton. There was a definite distention of the right ureter and suggestive changes in the left. Both ureters were well visualized, indicating a moderate stasis. A second x-ray (Fig. 1) was taken on the ninety-fourth day of pregnancy.



Fig. 1.—X-ray photograph showing distended ureter in a monkey on the ninety-fourth day of pregnancy. Interrupted line marks extent of uterus.

The distended right ureter was seen, but the uterine shadow was not large enough to be compatible with a normal gestation of this length and no fetal skeleton was evident. A hysterotomy was performed on the one hundredth day and the uterine contents removed as a whole. The placental size was comparable to that of a sixty-day pregnancy, but when the membranes were opened no fetus was found, although the point of attachment of the cord was easily recognized. The amniotic fluid contained some debris. In this instance, even after spontaneous absorption of the fetus, the hydroureter persisted because of the presence of a functioning placenta. At eleven days post partum, the ureters were normal in size.

Monkey B.—This animal matured in the colony, menarche on Sept. 30, 1938. The first ovulation was recorded as having taken place a few days before a laparotomy performed six months later on March 14, 1939. The first pregnancy began November 8 and is the one of

interest here. The animal was in a group being studied for the character of ureteral response in known first pregnancies. An x-ray film on the thirty-sixth day visualized the ureters, which were normal in caliber for the nonpregnant animal, but the unbroken columns of fluid indicated placental activity. Three weeks later, on day fifty-nine, these columns were seen to have doubled their width, indicating a beginning of dilatation. The fundus of the uterus reached the lower border of the seventh vertebra and the pregnancy, as disclosed in these two x-ray pictures, appeared to be progressing normally. However, on the eighty-eighth day the uterine shadow, which then extended to the upper border of the seventh vertebra, did not contain any evidence of a fetal skeleton. An x-ray picture taken of this animal on the eightieth day of a normal pregnancy during the following year was used for comparison and in the normal picture the uterus was larger reaching the central zone of the fifth vertebra. In the normal pregnancy the outlines of the skull and facial bones lay to the right of the sixth lumbar vertebra with the axial skeleton of the fetus distinguishable between the seventh vertebra and the crest of the ilium. Ureteral distention was definitely less than in the pathologic pregnancy under examination here in which there was a much smaller uterus. A hysterotomy was performed upon the one hundred twenty-seventh day in order to recover and examine the uterine contents. Without opening up the amniotic cavity, the placenta with its membranes was dissected from the uterine wall and placed in formalin to harden before opening. The embryo measured 25 mm. When the length of the embryo was taken with its physical appearance and reference made to Heuser and Streeter's⁶ work (1941), it was indicated that the stage of development reached was about the forty-sixth day. This agrees with data from our own series of fetuses. The placenta weighed 47 grams, a weight which is normally associated with a pregnancy of seventy-five days' duration. A fetus compatible with a seventy-five day pregnancy should measure about 90 mm. (Schultz⁷) in length instead of the aforesaid 25 mm. and so it appears that the failure began in the embryo while the placenta continued to function, in part. To summarize, in this animal there was an established ureteral dilatation on the fifty-ninth day, two weeks after the death of the fetus, and the dilatation persisted through the eighty-eighth day, or seven weeks after the fetal death, and up to eleven weeks later to the time of the hysterotomy on the one hundred twenty-seventh day. Thus, the living, functioning placenta sustained the physiological state of pregnancy with its accompanying hydroureter for 81 days after the death of the embryo.

Monkey C.—Born in the laboratory May 21, 1937, the first pregnancy of this animal began Feb. 4, 1940. On the ninety-fourth day the urogram showed columns of fluid with some distention of the ureter. There was no fetal skeleton and the uterine fundus reached only to the upper part of the body of the sixth vertebra. The diagnosis of fetal death before the seventieth day was made. The animal was kept under close observation, especially when vaginal bleeding began on the one hundred twenty-first day. Twenty-four hours later it was possible to recover the products of the spontaneous, complete abortion. On examination it was found that the primary and secondary lobes of the placenta were well defined, but the ovum was represented by a pear-shaped solid mass 1.5 cm. in diameter within a collapsed amniotic sac. The size of the placenta indicated comparatively normal growth to about the sixtieth day. The embryo gave no clue to the stage reached before degeneration, but the well-defined placenta indicates embryonic normality for fifty days or more. It is of interest to compare the ureteral dilatation of this pregnancy with that of the succeeding one. Comparison was made with a urogram of the one hundred forty-eighth day from the second pregnancy. At this time the height of ureteral distention for the pregnancy should be reached and it was interesting to find that, even in the presence of a comparatively large fetus, the dilatation was less in degree than in the first pregnancy at ninety-four days with a degenerated fetus.

Discussion

When hormone assay methods were first available, Frank,⁸ 1929, studied a case in which the placenta had remained in the uterus for eighteen days following an otherwise normal delivery. Before manual removal of the placenta the

estrogen level of the blood was found to be characteristic of pregnancy. In a study of an abdominal pregnancy after a term fetus had been removed and while of necessity the placenta had been left attached to the viscera, Ware and Main,⁹ 1934, showed that the patient remained physiologically pregnant for over a month following removal of the infant. At the end of that time the urine assays for prolan became negative and it was assumed that the placenta had been absorbed.

Zondek¹⁰ has recently described a human case in the eighth month of pregnancy in which fetal movements had ceased—no fetal heart sounds were heard and death of the fetus was diagnosed. Hormonal tests, however, showed that the level of estrogenic hormone in the serum corresponded to that of normal pregnancy, and the gonadotropin level of the urine was also high. These values fell only after operative removal of a dead fetus with a placenta normal in appearance. The work⁴ from our laboratory has shown that after operative removal of the fetus the estrogenic levels were maintained until spontaneous expulsion of the placenta, after which the estrogens fell abruptly but the androgens, coming in greater part presumably from the adrenals, returned more slowly to the nonpregnant levels. Zondek says, in remarking on the fact that the placenta can sometimes remain functional in spite of death of the fetus, "In such cases the hormone levels in blood and urine can be higher than in normal pregnancy because the entire output of placental hormones is taken up by the maternal circulation, none going to the fetus." In this connection it is interesting to note the early appearance of dilatation present on the fifty-ninth day in Monkey B.

Within the last year Hirsch¹¹ has described a case of convulsive eclampsia in which all signs and symptoms developed after death of the fetus. He warned against complacency, even though the fetus was known to be dead because the placenta might still be active.

Evidence for the functional independence of the placenta, once pregnancy is well started, is imposing. It has long been known that ovaries are not necessary for the completion of pregnancy in the human being and Hartman and Corner¹² have recently, in the monkey, pushed back the crucial time for removal of the ovaries (corpus luteum) to the first month of the six-month gestation. In the same animal it has been shown¹ that the operative removal of the fetus or the fetus with one or both ovaries does not interrupt pregnancy; thyroidectomy is compatible with the continuance of gestation and, in some animals finally, P. E. Smith¹³ has shown that the hypophysis is not necessary for the continuation of pregnancy. A comprehension of the autonomy of the placenta has developed with the accumulation of data from the field of endocrinology.

Summary

Upper urinary tract dilatation has been demonstrated in the monkey after death of the fetus, but while the placenta remained functional toward the maternal organism. The unruptured uterine contents were secured at hysterotomy in two instances and recovered at the time of a spontaneous abortion in the third.

These three histories of primary death of the fetus parallel earlier experiments in which the fetus alone was surgically removed. Thus, pyeloureteral dilatation in pregnancy is associated with the functioning of the maternal surface of the placenta during the physiological state of pregnancy without dependence on the continued presence or life of the fetus.

Grateful acknowledgment is made to Mr. Joseph Negri for management of the monkey colony, and to Miss Janet Buchanan and Miss Helen Carlson for the excellent urographs.

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A STATISTICAL REPORT OF 1,771 CASES OF HYSTERECTOMY

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ON THREE previous occasions, statistics on hysterectomy have been presented from this department.¹⁻³ This fourth report comprises 1,771 consecutive cases covering the five-year period ending Jan. 1, 1945. The pan- or total hysterectomy as described by W. H. Weir⁴ has been the procedure of choice.

As seen in Table I, panhysterectomy was done in 71 per cent of the cases. This is slightly lower than in our previous series, due to the recent popularity of the vaginal hysterectomy, which shows a proportional increase. The supravaginal hysterectomy was done on only the most complicated cases by the resident staff, but continues to be a routine procedure by a few of the visiting staff, which accounts for the relatively high number in the latter group. Although the proportion of white to Negro in the community as a whole is ten to one, 30 per cent were Negro patients. This is due to the

TABLE I. DISTRIBUTION OF CASES

| | 179 | | 319 | | 1,273 | | 1,771 | |
|------------------------------|--------------|----------|--------------|----------|--------------|----------|-------|----------|
| | VAGINAL | | SUPRAVAGINAL | | PAN- | | TOTAL | |
| | HYSTERECTOMY | | HYSTERECTOMY | | HYSTERECTOMY | | | |
| | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| <i>Distribution.</i> — | | | | | | | | |
| Resident staff | 82 | 4.63 | 59 | 3.33 | 580 | 32.7 | 721 | 40.7 |
| Visiting staff | 97 | 5.48 | 260 | 14.7 | 693 | 39.2 | 1,050 | 59.3 |
| Combined staffs | 179 | 11.1 | 319 | 18.0 | 1,273 | 71.0 | 1,771 | 100.0 |
| <i>Color distribution.</i> — | | | | | | | | |
| White | 159 | 88.8 | 258 | 80.9 | 822 | 64.5 | 1,239 | 69.9 |
| Negro | 20 | 12.2 | 61 | 19.1 | 451 | 35.5 | 532 | 30.1 |
| <i>Parity.</i> — | | | | | | | | |
| Para 0 | 6 | 3.4 | 138 | 43.4 | 413 | 32.4 | 557 | 31.4 |
| Para 1 plus | 173 | 96.6 | 181 | 56.6 | 860 | 67.6 | 1,214 | 68.6 |

greater incidence of myoma and pelvic inflammation in this group and to the particular district from which the out-patient clinic draws the majority of its cases. The greater proportion of parous patients is again found in the vaginal hysterectomy group where prolapse resulting from childbirth is the most frequent indication for this procedure. As a supravaginal hysterectomy is usually done only in the presence of a normal-appearing cervix, a comparatively larger number of nonparous women are found in this group.

The age distribution is given in Table II. The largest proportion of the pan- and supravaginal hysterectomies occurs in women nearing or at the menopause, namely, in the fourth and fifth decades of life. This is due to many factors including the increase in symptoms from pathologic lesions of

the pelvic organs at this age, the often elective nature of this operation, and the desire to preserve the reproductive function by most women as long as possible. As prolapse is usually a late complication of childbirth, vaginal hysterectomy is done more often in the later decades.

TABLE II. AGE DECADE DISTRIBUTION

| YEARS | 179 VAGINAL HYSTERECTOMY | | 319 SUPRAVAGINAL HYSTERECTOMY | | 1,273 PAN- HYSTERECTOMY | | 1,771 TOTAL | |
|--------------------------|--------------------------------|------|-------------------------------------|------|-------------------------------|------|----------------|------|
| | NO. | CENT | NO. | PER | NO. | PER | NO. | PER |
| | | PER | | CENT | | CENT | | CENT |
| Second decade, 10 to 19 | 0 | 0 | 1 | .31 | 5 | .39 | 6 | .28 |
| Third decade, 20 to 29 | 2 | 1.1 | 18 | 5.6 | 73 | 5.7 | 93 | 5.2 |
| Fourth decade, 30 to 39 | 27 | 15.1 | 131 | 41.0 | 540 | 42.4 | 698 | 39.4 |
| Fifth decade, 40 to 49 | 48 | 26.8 | 136 | 42.6 | 542 | 42.6 | 726 | 41.0 |
| Sixth decade, 50 to 59 | 57 | 31.8 | 27 | 8.5 | 90 | 7.1 | 174 | 9.8 |
| Seventh decade, 60 to 69 | 39 | 21.8 | 6 | 1.9 | 22 | 1.7 | 67 | 3.8 |
| Eighth decade, 70 plus | 6 | 3.4 | 0 | 0 | 1 | .08 | 7 | .4 |

Chronic cervicitis has been excluded from the list of diagnoses given in Table III because its presence was reported by the pathologist in almost every case in which the cervix was examined. Myoma and relaxation of the vaginal outlet again are the most common indications for hysterectomy. The incidence of salpingitis has not appreciably decreased as yet as a result of penicillin and the sulfonamides, because old, chronic cases originating before the advent of these drugs were most often encountered. The diagnosis of endometriosis was not confirmed by the pathologist in many cases but was made clinically at the time of operation, on finding extensive and characteristic scar tissue from which the islands of endometrial-like glands had long since disappeared. The four instances of carcinoma of the cervix were diagnosed postoperatively.

TABLE III. INCIDENCE OF DIAGNOSIS

| | 179 VAGINAL HYSTERECTOMY | | 319 SUPRAVAGINAL HYSTERECTOMY | | 1,273 PAN- HYSTERECTOMY | | 1,771 TOTAL | |
|------------------------|--------------------------------|------|-------------------------------------|------|-------------------------------|------|----------------|------|
| | NO. | PER | NO. | PER | NO. | CENT | NO. | PER |
| | | CENT | | CENT | | PER | | CENT |
| Relaxed vaginal outlet | 172 | 96.0 | 95 | 29.8 | 635 | 49.8 | 902 | 52.0 |
| Myoma | 61 | 34.0 | 258 | 89.3 | 897 | 70.5 | 1,216 | 68.5 |
| Salpingitis | 1 | .56 | 93 | 29.2 | 375 | 34.0 | 469 | 26.5 |
| Endometriosis | 10 | 5.6 | 56 | 17.6 | 176 | 13.8 | 242 | 13.7 |
| Ovarian tumors | 1 | .56 | 26 | 8.1 | 58 | 4.5 | 85 | 4.8 |
| Carcinoma of fundus | 2 | 1.1 | 7 | 2.2 | 24 | 1.9 | 33 | 1.9 |
| Carcinoma of cervix | 0 | 0 | 1 | .31 | 3 | 0.2 | 4 | 0.2 |
| Prolapse | 165 | 92.2 | 7 | 2.2 | 111 | 8.7 | 283 | 16.0 |

TABLE IV. DISTRIBUTION OF MOST COMMON SYMPTOMS

| | 179 VAGINAL HYSTERECTOMY | | 319 SUPRAVAGINAL HYSTERECTOMY | | 1,273 PAN- HYSTERECTOMY | | 1,771 TOTAL | |
|----------|--------------------------------|------|-------------------------------------|------|-------------------------------|------|----------------|------|
| | NO. | PER | NO. | PER | NO. | PER | NO. | PER |
| | | CENT | | CENT | | CENT | | CENT |
| Pain | 123 | 68.7 | 229 | 71.8 | 872 | 68.5 | 1,224 | 69.1 |
| Bleeding | 33 | 18.4 | 142 | 44.5 | 580 | 45.5 | 775 | 42.6 |
| Tumor | 0 | 0 | 39 | 8.2 | 126 | 9.9 | 165 | 9.3 |
| Prolapse | 103 | 57.6 | 1 | .31 | 23 | 1.8 | 127 | 7.2 |

completely emptying the bladder. This is determined by catheterizing the patient daily after voiding and (measuring the results) installing 30 c.c. of 5 per cent Argyrol until less than an ounce is obtained by catheter. This procedure avoids later infections in the bladder from residual urine, and affords great comfort to the patient.

It is apparent that the older the patient the longer the duration of the symptoms, the greater the pathology, and the lower the chances for a complete cure. Therefore, cystoceles and rectoceles and their associated pelvic pathology should be anatomically corrected soon after the completion of the family, or about 40 years of age, so that the mother can be spared the long years of debilitating symptoms and be more healthy and better able to assure properly her responsibilities of middle life.

TABLE VII. POSTOPERATIVE COMPLICATIONS

| | 179 VAGINAL HYSTERECTOMY | | 319 SUPRAVAGINAL HYSTERECTOMY | | 1,273 PAN- HYSTERECTOMY | | 1,771 TOTAL | |
|-----------------------|--------------------------------|-------------|-------------------------------------|-------------|-------------------------------|-------------|----------------|-------------|
| | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| Infected wound | 1 | .56 | 12 | 3.76 | 36 | 2.8 | 49 | 2.8 |
| Peritonitis | 3 | 1.7 | 2 | .62 | 8 | .63 | 13 | .73 |
| Phlebitis | 1 | .56 | 1 | .31 | 12 | .94 | 14 | .79 |
| Vesicovaginal fistula | 0 | 0 | 0 | 0 | 2 | .16 | 2 | .11 |
| Rectovaginal fistula | 1 | .56 | 0 | 0 | 2 | .16 | 3 | .17 |
| Pulmonary embolus | 3 | 1.7 | 2 | .62 | 9 | .71 | 14 | .79 |
| Cystitis | 16 | 8.3 | 11 | 3.4 | 46 | 3.6 | 73 | 4.1 |
| Pyelitis | 1 | .56 | 2 | .62 | 3 | .24 | 6 | .34 |
| Pneumonia | 3 | 1.7 | 1 | .31 | 14 | 1.1 | 18 | 1.0 |
| Paralytic ileus | 2 | 1.1 | 7 | 2.2 | 21 | 1.7 | 30 | 1.7 |
| Hemorrhage | 2 | 1.1 | 2 | .62 | 12 | .94 | 16 | .9 |

TABLE VIII. MORBIDITY

| | 179 VAGINAL HYSTERECTOMY | | 319 SUPRAVAGINAL HYSTERECTOMY | | 1,273 PAN- HYSTERECTOMY | | 1,771 TOTAL | |
|--|--------------------------------|-------------|-------------------------------------|-------------|-------------------------------|-------------|----------------|-------------|
| | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| Temperature below 38.5° C. | 74 | 41.4 | 170 | 53.3 | 763 | 59.9 | 1,007 | 56.8 |
| Temperature above 38.5° C. for one day | 39 | 21.7 | 82 | 25.7 | 257 | 20.2 | 378 | 21.3 |
| Temperature above 38.5° C. for more than one day | 66 | 36.9 | 67 | 21.0 | 253 | 19.9 | 386 | 21.8 |

The conventional method of reporting morbidity rates is used in Table VIII. It is not completely satisfactory because of the large number of cases which have a brief, twenty-four to forty-eight hour, but marked febrile reaction postoperatively, for which there is no adequate explanation. The morbidity in the vaginal hysterectomy group, because of the more advanced age of the patients, remains essentially the same as before and is higher than that found in the supravaginal and panhysterectomy groups. These are appreciably lower than those reported previously, due probably to the availability and more frequent use of the sulfonamides and penicillin.

TABLE IX. MORTALITY RATES

| | 179 VAGINAL HYSTERECTOMY | | 319 SUPRAVAGINAL HYSTERECTOMY | | 1,273 PAN- HYSTERECTOMY | | 1,771 TOTAL | |
|-----------------|--------------------------------|-------------|-------------------------------------|-------------|-------------------------------|-------------|----------------|-------------|
| | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| Resident staff | 0 | 0 | 2 | 4.08 | 8 | 1.38 | 10 | 1.37 |
| Visiting staff | 3 | 3.2 | 1 | .38 | 6 | .87 | 10 | .95 |
| Combined staffs | 3 | 1.68 | 3 | .93 | 14 | 1.10 | 20 | 1.13 |

The mortality rates are shown in Table IX. These compare favorably with similar series of hysterectomies and our last one. The mortality rates for supravaginal and panhysterectomies are approximately the same and for the vaginal hysterectomies only slightly higher. A brief summary of the

It is difficult to evaluate the frequency of the symptoms, due to their variety and their subjective character. Those tabulated in Table IV are, at best, only an estimation. Urinary symptoms, although found very frequently and, in few cases, as the primary one, were excluded because they are most often secondary.

Additional operative procedures at the time of hysterectomy are not only frequently desirable but are often necessary. The incidence in this series is shown in Table V. To obtain the best clinical result by providing adequate pelvic support, the repair of the relaxed vaginal outlet is considered of primary importance in this clinic. The frequency of repair procedures approximates the incidence of relaxed vaginal outlets and approaches that of parous women. As active infection is rare in this type of pelvic surgery, appendectomy is not only desirable but can be easily done and frequently is.

TABLE V. ADDITIONAL OPERATIVE PROCEDURES

| | 179 VAGINAL HYSTERECTOMY | | 319 SUPRAVAGINAL HYSTERECTOMY | | 1,273 PAN- HYSTERECTOMY | | 1,771 TOTAL | |
|-------------------------------|--------------------------------|-------------|-------------------------------------|-------------|-------------------------------|-------------|----------------|-------------|
| | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| Curettage | 4 | 2.24 | 29 | 9.1 | 50 | 3.9 | 83 | 4.7 |
| Perineorrhaphy | 174 | 97.2 | 90 | 28.2 | 620 | 48.6 | 884 | 49.9 |
| Anterior colporrhaphy | 177 | 98.8 | 35 | 11.0 | 291 | 22.8 | 503 | 28.4 |
| Partial removal of adnexa | 4 | 2.24 | 128 | 40.1 | 414 | 32.4 | 546 | 30.8 |
| Complete removal of adnexa | 1 | .56 | 46 | 14.4 | 260 | 20.4 | 307 | 17.3 |
| Appendectomy (possible) | 0 | 0 | 159 | 68.5 | 862 | 86.3 | 1,021 | 82.9 |
| Hemorrhoidectomy | 26 | 14.5 | 23 | 7.2 | 83 | 6.5 | 132 | 7.5 |
| Cholecystectomy | 0 | 0 | 0 | 0 | 1 | .08 | 1 | .06 |

Injury to the bowel or bladder at the time of operation, though infrequent, as seen in Table VI, is seldom serious. On the other hand, a cut or tied ureter is the most feared operative complication of hysterectomy. Consciousness of this danger has kept the incidence very low, although it is slightly higher here, when compared with our previous five-year period. Contrary to the popular belief of the general surgeon, its occurrence is no higher in the pan- or total hysterectomy than it is in the supravaginal.

TABLE VI. OPERATIVE COMPLICATIONS

| | 179 VAGINAL HYSTERECTOMY | | 319 SUPRAVAGINAL HYSTERECTOMY | | 1,273 PAN- HYSTERECTOMY | | 1,771 TOTAL | |
|----------------|--------------------------------|-------------|-------------------------------------|-------------|-------------------------------|-------------|----------------|-------------|
| | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| Injured ureter | 1 | .56 | 3 | .93 | 7 | .55 | 11 | .62 |
| Torn bladder | 0 | 0 | 0 | 0 | 8 | .63 | 8 | .45 |
| Torn bowel | 2 | 1.1 | 2 | .62 | 5 | .39 | 9 | .51 |

Various postoperative complications are enumerated in Table VII. They are all relatively infrequent. While the incidence of infected wounds and cystitis is lower, the others remain essentially the same as in the previous five-year period and are again approximately the same in the supravaginal and panhysterectomies. Paralytic ileus, which is now more easily recognized and treated, was a complication in 1.7 per cent of the cases.

THE RATE OF RENEWAL IN WOMAN OF THE WATER AND SODIUM OF THE AMNIOTIC FLUID AS DETERMINED BY TRACER TECHNIQUES

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ALTHOUGH the injection of dyes has demonstrated that exchange of an artificial constituent of the amniotic fluid may take place with the maternal plasma,^{1, 2} it was impossible to obtain a reliable and precise picture of the dynamics of the naturally occurring constituents of the fluid until radioactive and stable isotopes became available for experimental purposes. Measurements made with the isotope technique in the guinea pig showed that the water of the fluid at all stages of gestation is completely replaced at the surprisingly rapid rate of about once an hour, whereas the rate of replacement of the sodium is about fifty times slower.³ We have now measured water and sodium transfer to the human amniotic fluid using deuterium oxide (heavy water) and radioactive sodium (Na^{24}) as the tracer substances. The observations with water were made on five women, and with sodium on twenty women, on whom hysterotomies were performed for the reasons given in Tables I and II.

Methods

The cases in this series are the same as those used in measurement of placental transfer of water and sodium to the fetus; and details of the techniques employed can be found in the reports of those studies.^{4, 5} The essential points are: (1) A sample of amniotic fluid was withdrawn through the wall of the intact uterus with needle and syringe approximately thirty minutes after intravenous injection of NaCl tagged with Na^{24} , and ten minutes after intravenous injection of deuterium oxide (D_2O). (2) Care was taken to avoid contamination of the fluid with blood. (3) The rate of disappearance of the tracer substance from the maternal blood plasma was determined for the tagged sodium and D_2O in order to permit calculation of the average concentration of the tracer during the period of transfer to the amniotic fluid. The D_2O content of each sample of amniotic fluid was determined in duplicate; checks to within ± 0.01 per cent were obtained. Because of the low concentration of tagged sodium, radioactivities were measured on samples of 5 c.c. of amniotic fluid or, in some cases, on larger samples concentrated by evaporation; correction was made for absorption of radiation by the sample.⁶

The methods and rationale for calculating the rate of transfer of water and sodium to the fetus have been given.^{4, 5} Similarly, the amount of water trans-

primary cause of death is as follows: Of the fourteen deaths following pan-hysterectomy, one was due to pneumonia, four to pulmonary embolus, four to peritonitis, and five were due to cardiac failure. Of the three deaths following supravaginal hysterectomy, one was due to pulmonary embolus, one to cardiac failure, and one to cerebral hemorrhage. Finally, of the three deaths following vaginal hysterectomy, one was due to pulmonary embolus, one to cerebral accident, and one to peritonitis.

In conclusion, statistics have been presented on a large number of consecutive hysterectomies for another five-year period from this department. Although it is generally conceded that, in trained hands, pan- or total hysterectomy as against supravaginal hysterectomy is the procedure of choice when the uterus is to be removed, our statistics again bear this out.

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the rapidly diminishing concentration of D_2O in the blood during the early part of the experiment. The method for obtaining this value has been reported.^{4, 5} In like manner the amount of sodium transferred to the amniotic fluid for the period of the experiment can be calculated from the equation:

$$Na_{amf} = Na_{amf}^* \times Na_{mp} \div Na_{mp}^*$$

where Na_{amf}^* refers to the sodium, tagged with the radioactive isotope, which is present in 1 c.c. of the amniotic fluid; Na_{mp}^* to the average concentration of tagged sodium in the maternal plasma and Na_{mp} to the concentration of normally occurring sodium in the maternal plasma. We have assumed the concentration of sodium in maternal plasma to be 3.3 mg. per cubic centimeter.⁷ The calculation of the rate at which the sodium of the amniotic fluid is replaced by sodium of the maternal plasma has been made on the assumption that there are 2.8 mg. sodium per c.c. amniotic fluid.⁸

Results

The results are presented in Tables I and II and call for little comment. On the average, 34.5 per cent of the water of amniotic fluid is replaced per hour by water from the maternal plasma. This means that the average rate of renewal of the water of the amniotic fluid is once every 2.9 hours. The sodium of the fluid is renewed at the average rate of 6.9 per cent of that present per hour; i.e., the sodium of the fluid is turned over once every 14.5 hours. There is considerable variation, apparently unrelated to gestational age, among the observed rates both for water and sodium.

Discussion

The rate at which water is transferred to the amniotic fluid is considerably greater than that for sodium. Whereas the amount of water which flows into and out of the amniotic sac in three hours is approximately equal to the volume of the amniotic fluid, only about one-fifth of the total sodium is replaced in the same interval. This means that water is renewed about five times as rapidly as sodium. When a comparison of the rates of transfer of water and sodium across the placenta in the guinea pig was made, a similar difference was noted.⁹ Evidence was given which could explain the observations completely on the basis of greater permeability of the placental membrane to water than to sodium. The same explanation, applied to whatever membranes are involved, may hold for the difference in transfer rates of water and sodium from the maternal circulation to the amniotic fluid.

It will be apparent from the large difference in rate of transfer of water and sodium to the amniotic fluid that it is impossible to make reliable deductions about the rate of exchange of the normal constituents of the fluid from observations on foreign substances like dyes.

The main source of the amniotic fluid has been thought by some investigators to be fetal urine. The present experiments shed no light as to the principal site at which the exchange of water and sodium between the maternal blood and amniotic fluid takes place. It was pointed out in studies on the guinea pig⁹ that in the earlier stages of pregnancy a volume of water equal to that of the fetus flows in and out of the amniotic sac in an hour, and that it would seem questionable that the fetal urine could alone account for this relatively large volume of fluid. The results in women substantiate this view. At the tenth week of gestation, for example, 40 c.c. of amniotic fluid may be associated with

TABLE I. RATE OF TRANSFER OF WATER FROM MATERNAL CIRCULATION TO AMNIOTIC FLUID.
"DELIVERY TIME OF AMNIOTIC FLUID" REFERS TO MINUTES AFTER INJECTION
OF D₂O INTO MOTHER

| INDICATION FOR OPERATION | GESTATION AGE WEEKS | DELIVERY TIME OF AMNIOTIC FLUID MINUTES | AVERAGE CONCEN- TRATION OF D ₂ O IN MATERNAL PLASMA PER CENT | CONCEN- TRATION OF D ₂ O IN AMNIOTIC FLUID PER CENT | H ₂ O TRANS- FERRED PER C.C. OF AMNIOTIC FLUID PER HOUR C.C. | PER CENT OF H ₂ O OF AMNIOTIC FLUID RENEWED PER HOUR |
|--------------------------------|---------------------------|---|---|---|---|--|
| Chorea | 14 | 7.5 | 0.616 | 0.029 | 0.376 | 37.6 |
| Psychiatric | 16 | 9.5 | 0.448 | 0.019 | 0.269 | 26.9 |
| Cardiac disease | 18 | 11.0 | 0.447 | 0.011 | 0.134 | 13.4 |
| Chronic pyelitis | 30 | 5.2 | 0.485 | 0.031 | 0.740 | 74.0 |
| Contracted pelvis | 40 | 7.1 | 0.411 | 0.010 | 0.206 | 20.6 |
| Average | | | | | | 34.5 |

TABLE II. RATE OF TRANSFER OF SODIUM TO AMNIOTIC FLUID FROM MATERNAL CIRCULATION.
"DELIVERY TIME OF AMNIOTIC FLUID" REFERS TO MINUTES AFTER INJECTION OF Na* INTO
MOTHER. THE RADIO-ACTIVITIES WERE MEASURED IN SAMPLES LARGER THAN 1 C.C. BUT ARE
PRESENTED IN THIS UNIT FOR CONVENIENCE. IN CALCULATING "PER CENT OF Na OF
AMNIOTIC FLUID RENEWED PER HOUR," IT WAS ASSUMED THAT 1 C.C. OF AMNIOTIC
FLUID CONTAINS 2.8 MG. Na (6)

| INDICATION FOR OPERATION | GESTA- TION AGE WEEKS | DELIVERY TIME OF AMNIOTIC FLUID MINUTES | Na* PER C.C. MATERNAL PLASMA (AVERAGE) MICROGRAMS | Na* PER C.C. AMNIOTIC FLUID MICROGRAMS | Na TRANS- FERRED PER C.C. AMNIOTIC FLUID PER HOUR MILLIGRAMS | PER CENT OF Na OF AMNIOTIC FLUID RENEWED PER HOUR |
|-----------------------------|--------------------------------|---|---|---|--|--|
| Previous section | 38 | 30 | 1.94 | 0.056 | 0.189 | 6.8 |
| Psychiatric | 16 | 25 | 1.31 | 0.025 | 0.151 | 5.4 |
| Psychiatric | 10 | 29 | 1.74 | 0.029 | 0.112 | 4.0 |
| Previous section | 37 | 26 | 5.98 | 0.079 | 0.101 | 3.6 |
| Previous section | 40 | 42 | 3.60 | 0.340 | 0.440 | 15.0 |
| Chorea | 14 | 28 | 3.23 | 0.022 | 0.048 | 1.7 |
| Contracted pelvis | 36 | 27 | 2.59 | 0.041 | 0.116 | 4.1 |
| Chronic pyelitis | 31 | 40 | 3.80 | 0.280 | 0.370 | 14.0 |
| Carcinoma, abdomen | 17 | 28 | 3.86 | 0.086 | 0.157 | 5.4 |
| Contracted pelvis | 40 | 27 | 5.22 | 0.127 | 0.179 | 6.4 |
| Epilepsy | 12 | 28 | 4.65 | 0.186 | 0.282 | 10.0 |
| Chronic nephritis | 12 | 30 | 5.84 | 0.030 | 0.034 | 1.2 |
| Hypertension | 16 | 28 | 4.00 | 0.044 | 0.078 | 2.7 |
| Hypertension | 24 | 26 | 0.61 | 0.013 | 0.164 | 5.8 |
| Hypertension | 20 | 26 | 4.00 | 0.130 | 0.240 | 8.6 |
| Hypertension | 38 | 28 | 3.02 | 0.170 | 0.398 | 15.0 |
| Pre-eclampsia | 18 | 27 | 0.30 | 0.007 | 0.171 | 6.1 |
| Pre-eclampsia | 31 | 29 | 6.10 | 0.380 | 0.420 | 15.0 |
| Cardiac disease | 19 | 27 | 5.20 | 0.084 | 0.119 | 4.3 |
| Cardiac disease | 18 | 33 | 2.25 | 0.034 | 0.091 | 3.3 |
| Average | | | | | | 6.9 |

ferred to 1 c.e. of amniotic fluid in a known interval of time can be calculated from the equation:

$$H_2O_{amf} = D_2O_{amf} \div D_2O_{mb}$$

where H_2O_{amf} represents the water transferred to 1 c.e. of amniotic fluid; D_2O_{amf} , the observed concentration of heavy water in the water of the amniotic fluid; D_2O_{mb} , the average concentration, during the period of the experiment, of heavy water in the water of the maternal blood. The average concentration of heavy water in the water of the maternal blood is used in the calculations because of

AN INVESTIGATION INTO THE INCIDENCE OF ABORTION IN BALTIMORE

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TO DETERMINE the incidence of abortion in the general population a number of studies have been made in the United States, mainly in large cities. A variety of methods have been used, and great caution must be exercised in interpreting the data. One method employed by several investigators is to determine the number of abortions among the previous pregnancies of a series of obstetric patients, seen at the office or dispensary or admitted to a hospital. This method has the great advantage that questions as to the number and outcome of previous pregnancies are generally accepted as a routine part of the examination, and that there is usually good rapport between the patient and the physician in whom she has a high degree of confidence. To duplicate these conditions is often difficult in other types of studies. The outstanding deficiency of all obstetric series is that no pregnancy will be included unless it is followed by another which brings the case into the investigation. If abortions tend to occur more frequently among last pregnancies they will be underrepresented in the material. In addition, an obstetric series based upon the records of a single physician or a single hospital may be biased by the special professional interests of the doctor or the admission policies of the hospital.

The present paper is based on the case histories of all patients admitted to the Department of Obstetrics of the Johns Hopkins Hospital in Baltimore from 1937 to 1946 who had been pregnant at least once before.

The number of plurigravidas during the ten-year period was 10,397, and the aggregate number of their previous pregnancies 30,133 or 2.9 per patient. Of these 30,133 previous pregnancies 25,009, or 83.0 per cent, had produced a viable birth and 5,124, or 17.0 per cent, had ended in abortion. Unfortunately, it is not possible to say on the basis of the available data how many of these abortions were unintentional and how many were induced.

Of the 10,397 plurigravidas admitted to the service, 9,130, or 87.8 per cent, terminated their current pregnancy with a viable birth and 1,267, or 12.2 per cent, with an abortion. The greater part of these current abortions were probably unintentional, but an unknown number had been illegally initiated prior to admission, and a few were therapeutic. The 9,130 parturient women reported 25,558 previous pregnancies with 4,102, or 16.0 per cent, ending in abortion. On the other hand, the 1,267 aborting women had had 4,575 previous pregnancies, and 1,022, or 22.3 per cent, of these had ended in abortion. The abortion ratio is markedly higher among the previous pregnancies of aborting women than among the previous pregnancies of those who produced a viable birth. This relationship has also been observed by others. Abortions are underrepresented

a fetus weighing less than 20 Gm.⁸ and the water of this fluid will be completely replaced in about three hours. At term a fetus weighing 3.4 kg. is surrounded by approximately 1,000 c.c. of amniotic fluid which is exchanging water at the rate of approximately 350 c.c. per hour. This astonishingly rapid rate of replacement of the water of the human amniotic fluid, like that of the guinea pig, is at variance with the concept that the amniotic fluid is a relatively stagnant body fluid.

Summary

The rate of passage of water and sodium from the maternal circulation to the amniotic fluid has been measured with heavy water and radioactive sodium as the tracer substances. The water of the fluid is completely replaced on the average once every 2.9 hours; this considerable rate of turnover is at variance with the concept that the amniotic fluid is stagnant. The rate of transfer of water is about five times more rapid than that of sodium.

The heavy water for these experiments was purchased from a grant made by the Abbott Laboratories.

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The high abortion ratio observed among the private patients and the pattern by pregnancy order seen in this group suggest a population which controls its reproduction mainly by contraceptive methods, but without achieving complete success. In such a group many women will resort to induced abortion if a conception has occurred in excess of the number planned or at a time when it was not wanted. Those, on the other hand, who have had one or more unintentional abortions continue their efforts to have the number of babies they originally intended. Both mechanisms tend to produce a high abortion ratio which increases with the number of previous pregnancies.

The pattern among the Negroes, which is just the opposite from that seen in the private group, is an artefact resulting from the admission policies of the hospital. During the years covered by the present study, the number of hospital beds on the Negro ward has never been sufficient to accommodate all patients seeking admission and preference has been given—among others—to two categories: To those who had produced no previous viable birth and to those who had had very many. The effect of this policy has been to increase the abortion ratio among the secundigravidas and to reduce it among the multigravidas of the hospital material on which the study is based.

Summary

1. Report is made on 30,133 previous pregnancies of 10,397 patients on an obstetric service.
2. Of these pregnancies 5,124, or 17.0 per cent, ended in abortion.
3. The abortion ratio was higher among the previous pregnancies of aborting than of parturient women.
4. The abortion ratio was 25.1 per cent for private patients (white), 15.4 per cent for white ward patients, and 16.6 per cent for Negro patients.
5. With increasing number of previous pregnancies the abortion ratio increased for private patients, decreased for Negro patients, with no clear trend for white ward patients.

I want to thank Dr. Nicholson J. Eastman for his permission to use these records, and Mr. L. Omar Huesman for his aid in tabulating the data.

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among the current pregnancies terminated in the hospital. This makes the abortion ratio appear a little lower among the previous pregnancies of these patients than it actually is in the population from which they are drawn. Statistical methods have been devised to correct this bias. With the present material, however, the effect of the correction is so slight that it does not seem worth while to introduce it.

The total group of 10,397 patients can be broken down by color and pay status into three distinct components: 1,985 private patients, all of whom were white; 4,041 white ward patients; and 4,371 Negro ward patients. The aggregate numbers of previous pregnancies and the numbers and percentages of abortions in the three groups are presented in Table I, showing separately the findings for parturient and aborting women.

TABLE I. NUMBER OF WOMEN, OF PREVIOUS PREGNANCIES, AND OF ABORTIONS AND PER CENT OF PREGNANCIES ENDING IN ABORTION, BY COLOR AND PAY STATUS AND OUTCOME OF CURRENT PREGNANCY

| COLOR AND PAY STATUS | OUTCOME OF CURRENT PREGNANCY | NUMBER OF WOMEN | NUMBER OF PREGNANCIES | NUMBER OF ABORTIONS | PER CENT ABORTIONS |
|----------------------|------------------------------|-----------------|-----------------------|---------------------|--------------------|
| Private (White) | viable birth | 1,779 | 2,734 | 647 | 23.7 |
| | abortion | 206 | 425 | 146 | 34.4 |
| | | 1,985 | 3,159 | 793 | 25.1 |
| White ward | viable birth | 3,518 | 9,816 | 1,395 | 14.2 |
| | abortion | 523 | 2,036 | 432 | 21.2 |
| | | 4,041 | 11,852 | 1,827 | 15.4 |
| Negro ward | viable birth | 3,833 | 13,008 | 2,060 | 15.8 |
| | abortion | 538 | 2,114 | 444 | 21.0 |
| | | 4,371 | 15,122 | 2,504 | 16.6 |

The findings of the present study are in line with the results of earlier investigations.^{1, 3} In view of the difference in method it is doubtful how comparable they are with Anna Rochester's figures for Baltimore.² Her data were based upon a citywide sample of births in 1915, and the reported ratio of previous pregnancies ending in abortion was 7.5 per cent for white and 11.3 per cent for Negro women.

TABLE II. PER CENT OF PREVIOUS PREGNANCIES ENDING IN ABORTION BY COLOR AND PAY STATUS AND NUMBER OF PREVIOUS PREGNANCIES PER WOMAN

| PREVIOUS PREGNANCIES | PRIVATE (WHITE) | WHITE WARD | NEGRO WARD |
|----------------------|-----------------|------------|------------|
| One | 17.1 | 13.0 | 22.7 |
| Two | 26.9 | 15.1 | 19.2 |
| Three | 30.9 | 15.3 | 20.3 |
| Four | 34.6 | 16.0 | 21.1 |
| Five | 36.8 | 15.7 | 16.2 |
| Six | 41.7 | 15.7 | 13.8 |
| Seven or more | 41.5 | 16.2 | 13.5 |

Table II presents abortion ratios for the three color and pay status groups by the number of previous pregnancies per woman. A very striking pattern emerges. Among the private patients the abortion ratio increases steeply with increasing number of previous pregnancies. In the white ward group no clear trend is apparent. Among the Negroes the abortion ratio is seen to decrease with increasing number of pregnancies.

CHANGING CONCEPTS IN CERVICAL BIOPSY*

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A SERIES of seven cases of equivocal lesions of the cervix are presented. Six of these cases represent all of the lesions in which a problem in diagnosis was encountered by members of the staff in a series of 110 routine biopsies of the cervix performed in a six-month period. Two of these cases are considered to be benign (1 and 2), three intraepithelial carcinoma (3, 4, and 5), one early invasive carcinoma (6), and one both intraepithelial and early invasive carcinoma (7). These diagnoses are not concurred in by all of the members of the staff or by consultants whose opinions were requested.

Warnings as to the possible dangers of erroneous diagnosis of equivocal lesions of the cervix have been sounded before in the literature. TeLinde and Galvin¹ have stated, "The inability of pathologists to diagnose with certainty extremely early lesions has resulted in mistakes of a serious nature. Errors are made in both directions. Benign cancerlike lesions, the result of squamous cell metaplasia and epidermidization, are frequently erroneously called malignant. Early malignant lesions are also not infrequently called benign. Often, when dealing with these cancerlike lesions, the pathologist is in doubt, and he attempts to mask his lack of knowledge by calling them precancerous. This results in unnecessary surgery or irradiation." The failure to realize the relationship of intraepithelial carcinoma to invasive carcinoma, if complete study of the cervix is not attempted in cases where the original biopsy shows only intraepithelial carcinoma, is demonstrated by these authors. Ten cases were reported in which intraepithelial carcinoma of the cervix was treated by removal of the cervix with subsequent finding of definite invasive carcinoma. An eleventh case is reported in which the biopsy specimen showed the only area of invasions, but the removed cervix showed extensive changes in the surface epithelium such as were seen in the biopsies of the other ten cases. In none of these cases was the diagnosis of cancer possible from the palpation or inspection of the cervix.

The seven cases of equivocal lesions presented here were managed as follows:

| | | |
|---------|---------------------------|--|
| Case 1. | Benign lesion | Multiple biopsy. |
| Case 2. | Benign lesion | Scalpel conization. |
| Case 3. | Intraepithelial carcinoma | Rebiopsy, total hysterectomy. |
| Case 4. | Intraepithelial carcinoma | Irradiation (radium and deep x-ray). |
| Case 5. | Intraepithelial carcinoma | Rebiopsy, total hysterectomy. |
| Case 6. | Invasive carcinoma | Rebiopsy (curette), total hysterectomy, irradiation (deep x-ray only). |
| Case 7. | Invasive carcinoma | Scalpel conization, irradiation (radium and deep x-ray). |

*Read before the Central Association of Obstetricians and Gynecologists on Oct. 24, 1947, in Louisville, Ky.

Rh SENSITIZATION IN A PRIMIPARA CAUSED BY INTRAMUSCULAR INJECTION OF HUMAN SERUM RESULTING IN FATAL ERYTHROBLASTOSIS

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IT IS now generally recognized that transfusions, or even intramuscular injections of Rh-positive blood are far more potent in sensitizing Rh-negative individuals than is pregnancy with Rh-positive fetuses. Thus, while only one of about 25 Rh-negative women bearing Rh-positive babies becomes sensitized to the Rh factor, fully one-half of such individuals can be sensitized by injections of Rh-positive blood.¹ This difference is readily explained by the difference in quantity of antigen injected. On the other hand, it has been generally believed up to now that such sensitization could not result from the injection of serum or plasma, which is presumably free of red cells.

The purpose of this report is to present possibly the first case which demonstrates that such sensitization can occur after intramuscular injection of serum, causing fatal erythroblastosis even in a firstborn infant.

Case Report

Mrs. B. G., aged 24 years, was first seen by one of us (J.T.W.) on Jan. 30, 1947, in the fifth week of her pregnancy. Routine antenatal Rh test revealed that she was Rh negative, her husband Rh positive. Careful inquiry elicited no history of her having had either transfusions or injections of whole blood during infancy, childhood, or adult life. However, in discussing the matter with her father, who is a physician, he recalled that she had once had an intramuscular injection of pooled adult serum as a prophylactic measure against poliomyelitis. This had been given in October, 1931, when she was 8 years of age. The serum had been collected, prepared, and given by our own serologist as follows:

Twenty cubic centimeters of whole blood were drawn from each of six adult donors. Each specimen was "Wassermannized"; they were then centrifuged individually to obtain the serums which were pooled. The pooled serum was diluted with normal saline to make a solution of 40 per cent serum. Ten cubic centimeters of this solution were injected intramuscularly into each buttock.

Though it has been thought in the past that serum alone would not cause the production of Rh antibodies in Rh-negative individuals, she was nevertheless submitted to a more complete study which showed the following:

| Blood of | Group | M-N Type | Rh-Hr Type* | |
|--------------------|----------------|----------|--------------------|--|
| | | | Phenotype | Genotype |
| Prospective father | O | M | Rh ₊ rh | R ² r, R ² R ⁰ or r ⁺ R ⁰ |
| Prospective mother | A ₁ | MN | rh | rr |

*The M-N types are not important clinically, but are included for the sake of completeness. For a detailed description of the Rh-Hr types and their heredity see publications of Wiener.^{2, 3}

These results confirmed the original report that the mother is Rh negative and her husband Rh positive. Moreover, the husband was *presumably* heterozygous for the Rh factor as determined by tests with anti-Hr" serum.*

These tests were first made in the seventh week of pregnancy. At that time it was already possible to demonstrate the presence of Rh antibodies in the prospective mother's serum. She was accordingly studied at intervals during her pregnancy with results recorded in Table I. Despite the administration of typhoid and pertussis vaccine for purposes of counter-immunization, the antibody titer rose as shown in Table I.

TABLE I. RESULTS OF Rh ANTIBODY TITRATION DURING PREGNANCY

| ANTIBODY TITER (UNITS) BY THE METHOD OF | | | | |
|---|------------------------------------|----------------------------------|-------------------------------|---|
| TIME OF TEST | AGGLUTINATION (IN SALINE MEDIA) | BLOCKING (IN SALINE MEDIA) | CONGLUTINATION (IN PLASMA) | CONGLUTINATION (IN ALBUMIN- PLASMA) |
| 7 weeks | 0 | | 1½ | 4 |
| 17 weeks | 0 | | 6 | 11 |
| 23 weeks | 0 | | 3 | 12 |
| 27 weeks | 0 | | 3½ | 16 |
| 31 weeks | 0 | 60 | | 1,400 |

Otherwise her pregnancy progressed entirely normally except for an anemia which responded even better than usual to iron therapy, until the thirty-second week. At this time the obstetrician was suddenly presented with the urgent problem of terminating the pregnancy at once in the interests of the baby because of a sudden extreme increase in the titer of the Rh antibodies in the maternal serum, and the serious probability that this might well be the only chance this patient might ever have of bearing a live baby. Clinically, the fetus appeared larger than would ordinarily be expected at this period of gestation, arousing the suspicion that it might already be suffering from fetal hydrops. X-ray showed only one fetus in utero and from the size of the bones, it was felt that it was a large fetus rather than an hydropic one. The vertex appeared to be somewhat extended. Vaginal examination showed the cervix to be long, very firm, and tightly closed. The presenting part was well down in the pelvic inlet, and on the right an orbital ridge and eye could be felt, making it essentially a brow presentation. Since termination of the pregnancy was solely in the interests of the baby, and since even the time consumed in a long labor might further damage the baby, with conditions so adverse to induction from below, cesarean section was performed under fractional spinal anesthesia without further delay. The baby was a living male which cried vigorously immediately after delivery and weighed 5 pounds, 5 ounces. Exsanguination transfusion was begun on the baby within fifteen minutes of delivery. The mother's postpartum course was uneventful.

In so far as the infant was concerned, it was planned to proceed with exsanguination transfusion at once without waiting for laboratory determinations or any other clinical data, because the antenatal serologic tests indicated that we were dealing with a severely affected infant who would have been stillborn had the pregnancy been allowed to proceed any further. Before the cesarean operation, therefore, 500 c.c. of blood were drawn from a Group A type rh donor and mixed with 60 c.c. of citrate solution in preparation for the transfusion. Two-fifths of the plasma was removed and replaced with saline solution.†

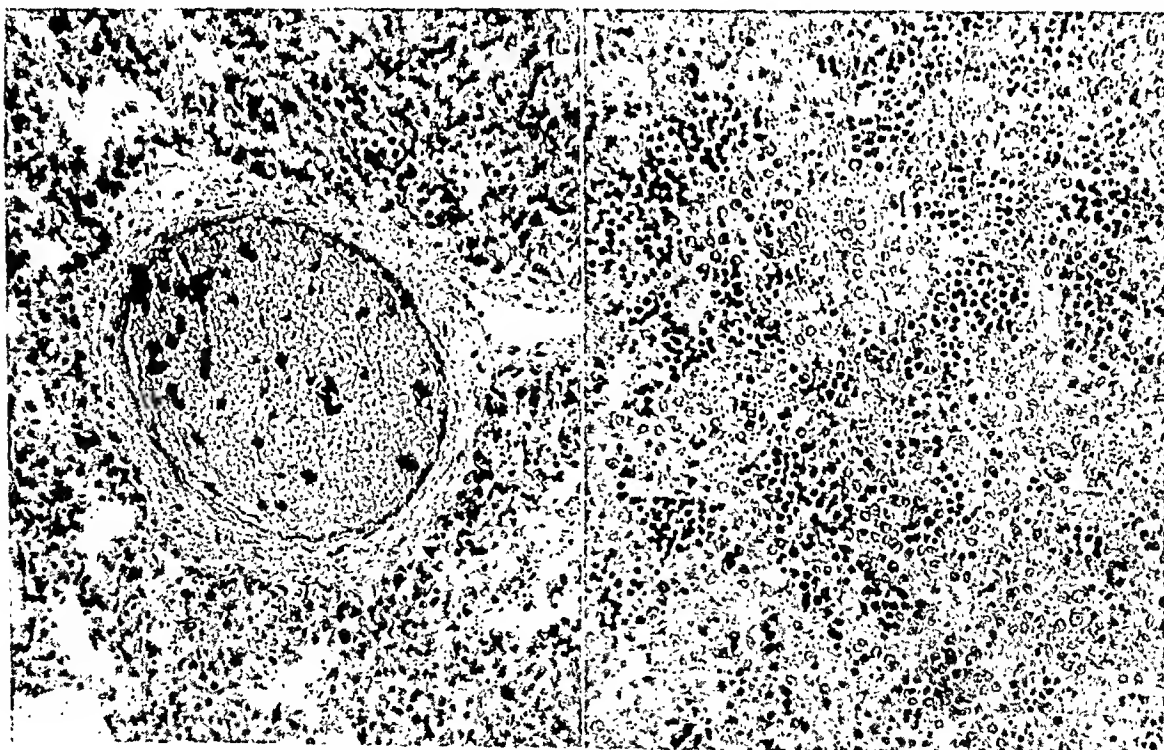
At birth no apparent abnormalities were noted except for pallor of the baby and marked icterus of the umbilical cord. The hemoglobin concentration, as subsequently reported, was only 44 per cent (6.4 Gm.) and the red blood cell count 1.21 million per cu. mm.

*The prospective father was Hr" positive as determined with serum kindly provided by Dr. A. E. Mourant.

†We have found that these babies do best if fresh blood rather than bank blood is used for the exchange transfusion. Since the prospective mother belonged to Group A and the father to Group O, we knew that a Group A donor would be compatible even before the baby was born.⁴ After experience with this and other similar cases we now use as much as 1,000 c.c. instead of 500 c.c. for replacement transfusion in such severely affected infants.⁵ This has proved more effective than the replacement of part of the donor's plasma with saline.

The baby was given oxygen. His tone and ery were good. As already mentioned, within fifteen minutes of delivery an exchange transfusion was started. During a two-hour period 380 c.e. of blood were injected into the left saphenous vein at the ankle, while 345 c.e. of blood were withdrawn from the right radial artery. The infant withstood the procedure well and seemed in good condition at its termination. He was then transferred to the nursery where he received newborn care and was placed in the incubator with continuous oxygen. The baby did not appear to be jaundiced. The liver and spleen were not palpable, and the hemoglobin concentration was now 80 per cent (11.6 grams).

Three and one-half hours after transfusion, definite jaundice was noted. The liver and spleen were palpable two and one-half fingerbreadths below the costal margin. The baby continued to be lively and had a good ery. The hemoglobin concentration had risen to 85 per cent (12.3 Gm.) by the time the baby was eight hours old. Physical examination was essentially as noted above except that the respirations were somewhat shallow and rapid. Because of the appearance of rapidly increasing jaundice which, in similar cases, we had previously found to indicate impending nuclear jaundice, an attempt was made to prevent intravascular coagulation of the remaining 15 per cent of the infant's blood cells, which had not been removed by the exchange transfusion, by instituting a continuous infusion of 15 c.e. of normal saline per hour. In addition 10 c.e. of blood were given each hour for five hours. This was effected through a "cutdown" in the right ankle vein.



A.

B.

Fig. 1.—(A) Section of lung showing small blood vessel plugged with erythrocytes. (B) Section of liver showing multiple islands of hematopoiesis.

The baby voided a scanty amount of deep yellow urine. He retained three feedings in eighteen hours after which all feedings were refused.

Physical examination twenty-four hours after birth showed the jaundice to be deeper with a reddish tinge. The hemoglobin concentration at that time was 100 per cent (14.5 grams). There was some edema of the thighs. The heart and lungs were normal. The

spleen was smaller and the liver was not felt. The baby was apparently doing well, when about one hour later he began having respiratory difficulties. The intermittent periods of apnea and cyanosis were treated with carbogen, coramine, and artificial respiration. A small amount of blood was noted coming from the right nostril.

Four hours later the infusion was discontinued, after a total volume of 180 c.c. of saline had been administered. The baby's extremities and eyelids were edematous at this time. Shortly after this (one-half hour) the infant was pronounced dead.

Subsequent tests confirmed the prediction that the baby was Rh positive (his complete classification was Group A, Type M, Type Rh₂). As a matter of fact, the blood cells failed to clump in anti-Rh₀ serum, but this was due to complete coating of the infant's cells by the maternal Rh-blocking antibodies as proved by the anti-globulin technique of Coombs and associates.⁶ In addition, the cord serum contained free univalent Rh-antibodies of a titer of 400 units by the albumin-plasma technique.⁷ The icterus index of the cord serum was 50 units by the acetone method, and the last sample obtained from the radial artery at the exchange transfusion had an icterus index of 38 units and Rh-antibody titer of 180 units. The fact that the icterus index and antibody titer did not decrease by 87 per cent in proportion to the replacement of red cells, can be explained, as pointed out in previous papers,⁸ by diffusion of bile and antibodies from the tissues into the circulation during the transfusion. In view of these extreme serologic findings, a fatal outcome was to be expected in spite of the exchange transfusion.⁸

The most significant gross postmortem findings were the large size of the placenta (760 Gm. or about one-third the weight of the infant), edema of the skin, generalized passive congestion, hepatosplenomegaly and edema of the brain with nuclear jaundice. The significant microscopic findings were disorganization of the liver cords with numerous large islands of hematopoiesis and plugging of the smaller blood vessels in the lungs by masses of red cells together with some erythroblasts.

Subsequently blood was obtained from the parents of the father and classified with the following results:

| Blood of | Group | M-N Type | Rh-Pr Type | |
|----------------------|-------|----------|---------------------------------|---|
| | | | Phenotype | Genotype |
| Paternal grandfather | O | M | Rh ₂ Rh ₂ | R ¹ R ² , r ¹ R ² or R ¹ r'' |
| Paternal grandmother | O | MN | rh | rr |

These findings proved that the father of the patient, previously found to belong to type Rh₂rh, is, with certainty, heterozygous. Repeat Rh-antibody titrations on the maternal serum two months post partum still showed a titer of about 1,000 units. Regarding future pregnancies, therefore, the following prediction can be made. There is an equal chance of future infants being either Rh positive or Rh negative. If Rh negative, naturally the infant will not be erythroblastotic; if Rh positive in view of the high maternal Rh-antibody titer it will be severely affected and so early in pregnancy that a stillbirth will be inevitable. Experience in similar cases indicates that it is unlikely that the Rh-antibody titer in this mother's serum will drop low enough during her childbearing period to enable her to have a viable Rh-positive fetus. Thus in future pregnancies we would be dealing with an all-or-none proposition with the outcome depending entirely on the Rh type of the fetus.

Summary and Conclusions

A case is reported in which a young primigravida is presumed to have been sensitized to the Rh factor by an injection of pooled human serum, given as a prophylactic measure against poliomyelitis during childhood, and in whose baby fatal erythroblastosis developed.

Accordingly, we should like to emphasize to clinicians that the injection of serum or plasma into Rh-negative women may create Rh sensitization. The hazard of such injections is at times as great as that accompanying the injection of Rh-positive whole blood, and may deprive even primiparas of the opportunity of having normal babies. Therefore, it is urgently recommended that in taking obstetric histories careful inquiry be made into whether or not

such injections have been received by the patient. It is likewise recommended that all physicians exercise utmost care and discretion in the use of these substances.

Since the preparation of this report, our attention has been called by personal inquiry from a California physician, to a second case of erythroblastosis in a firstborn baby whose mother may have been sensitized by injection of pooled serum as a prophylactic measure against poliomyelitis.

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80 HANSON PLACE

SULFADIAZINE CONCENTRATION IN THE BLOOD AND LOCHIA

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THIS study was undertaken to determine the amount of the sulfonamides excreted from the postpartum uterus and its relation to the blood concentration. The recent use of chemotherapy justifies this report. These patients were afebrile and the use of the sulfonamide was academic.

In this series of twenty-five patients, all but three were primiparas; two were gravida ii and one was gravida iii. Their prenatal and labor courses were normal. Each primipara was delivered by outlet forceps under pudendal block with mediolateral episiotomy.

Procedure

Sulfadiazine was started within twelve hours after delivery. The routine consisted of 60 grains initially and 15 grains every four hours, with equal amounts of sodium bicarbonate. Lochia was collected after twenty-four and forty-eight hours, and after seven days, by means of a contraceptive vaginal diaphragm. This diaphragm was inserted and removed with sterile technique.

It was found that the diaphragm has to be inserted four to five hours prior to the collection of the twenty-four and forty-eight specimens in order to obtain the necessary amount (8 to 10 c.c.) of lochia. Upon the removal of the diaphragm and its contents, blood was drawn from the cubital vein. Both specimens were collected in oxalated bottles. The seven-day lochia was collected by a diaphragm placed ten to twelve hours before, since the output at this postpartum period was minimal. This seven-day specimen was of particular interest because the lochia contained little blood, with an abundance of shreds and debris from the uterus.

All contents were kept refrigerated and taken to the Institute within twelve hours. The sulfadiazine levels were determined by the same technique, using the Bratton-Marshall Photometer technique.

Patients were ambulatory after the first postpartum day, save during the period of lochial collection. Only one tablet of Ergotrate, grain $\frac{1}{320}$, was given to each patient post delivery.

The sulfa concentrations in the blood were extremely variable for all groups, remaining proportionately similar in each case. Thus patient No. 2 revealed a level of 5.87 mg. per cent at the end of twenty-four hours, and 7.5 mg. per cent at the end of forty-eight hours. On the other hand, patient No. 14 had a blood level of 15.9 mg. per cent at the end of twenty-four hours and 14.2 mg. per cent at the end of forty-eight hours. Lochial concentrations behaved in a similar manner, though less in amount. Thus, in patient No. 2, the sulfonamide blood concentration at the end of twenty-four hours was 5.97 mg. per cent, while the lochial concentration was 4.74 mg. per cent. Again, patient No. 14 revealed a blood concentration of 18.9 mg. per cent at the end of twenty-four hours and a lochial concentration of 15.7 mg. per cent. Thus, if the concentration of the sulfadiazine was

high in the blood, we could expect high concentration in the lochia. This is true whether we study the twenty-four hour or the seven-day specimen (Table I).

There are paradoxical levels noted in the 48-hour specimen for patients No. 2, No. 3, No. 13, and No. 14, as well as in the seven-day specimen of patients No. 19, No. 21, and No. 25. In these, the diaphragm had to be retained for longer periods than the time allotted for the medication, because the lochia collected for the previous four to five hours and ten to twelve hours, respectively, was not sufficient for analysis. It would seem to indicate that a fairly rapid loss of sulfadiazine occurs in the blood stream, and, despite their ambulatory state, some patients still discharge small amounts of lochia.

The character of the lochia was no different than in the nonmedicated patients, although the odor tended to be "sharper." There were no complications in any of these patients, and all were discharged on the eighth postpartum day.

TABLE I

| PATIENT | 24 HOURS | | 48 HOURS | | 7TH DAY | |
|---------|----------------------------|-----------------------------|----------------------------|-----------------------------|----------------------------|-----------------------------|
| | BLOOD (MG. PER CENT) | LOCHIA (MG. PER CENT) | BLOOD (MG. PER CENT) | LOCHIA (MG. PER CENT) | BLOOD (MG. PER CENT) | LOCHIA (MG. PER CENT) |
| 1 | 12.19 | 9.45 | Specimen was lost | | | |
| 2 | 5.97 | 4.74 | 7.5* | 9.0 | | |
| 3 | 15.0 | 8.59 | 16.23* | 27.23 | | |
| 4 | 12.64 | 10.47 | Specimen lost | | | |
| 5 | 7.38 | 4.47 | 8.37 | 5.43 | | |
| 6 | 9.7 | 8.82 | 8.37 | 7.0 | | |
| 7 | 11.4 | 10.3 | 10.39 | 9.0 | | |
| 8 | 6.31 | 4.17 | 7.2 | 5.15 | | |
| 9 | 7.3 | 4.0 | 7.6 | 6.0 | | |
| 10 | 11.38 | 7.65 | 7.95 | 6.85 | | |
| 11 | 8.37 | 7.6 | 7.5 | 6.2 | | |
| 12 | 10.3 | 10.3 | 8.9 | 5.1 | | |
| 13 | 5.7 | 3.5 | 4.4* | 4.6 | | |
| 14 | 18.9 | 15.7 | 15.5* | 17.2 | | |
| 15 | 15.9 | 14.2 | 11.7 | 10.9 | | |
| 16 | | | | | 6.8 | 4.9 |
| 17 | | | | | 8.3 | 5.5 |
| 18 | | | | | 7.3 | 6.0 |
| 19 | | | | | 5.9* | 6.7 |
| 20 | | | | | 8.0 | 7.5 |
| 21 | | | | | 10.9* | 11.4 |
| 22 | | | | | 7.5 | 6.9 |
| 23 | | | | | 3.0* | 5.6 |
| 24 | | | | | 5.4 | 4.0 |
| 25 | | | | | 12.9* | 15.7 |

*See Discussion.

Summary

- 1. The sulfonamide concentration of the lochia paralleled the blood concentration in each instance.
- 2. The sulfadiazine routine of 60 grains initially and 15 grains every four hours results in extremely variable blood and lochial concentrations.
- 3. Ambulatory patients do not always reveal an increase in the amount of lochia.
- 4. The lochial odor of these patients tended to be "sharper" than that of those nonmedicated.

A FULL-TERM LIVE TUBAL PREGNANCY

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THIS 32-year-old, married, Negro para vii, gravida viii was admitted to Freedmen's Hospital at 3:55 p.m. July 18, 1947, on the request of her family physician, who had followed her prenatal course from approximately the third month in the Antepartum Clinic of a neighboring state. After following her labor in the home for a period of fourteen hours without progress, he sensed a complication necessitating hospitalization. On entrance, she showed evidence of delirium, exhaustion, and dehydration.

Her prenatal course was significant in that she complained throughout of abdominal pain. Interrogation localized this pain more to the left lower quadrant, gradually moving to the upper quadrant as the pregnancy progressed. She was referred to the Consultation Clinic during her sixth month for examination and x-ray. The consultant did not recognize any abnormality. Her last menses were Oct. 21, 1946, and her expected date of confinement July 28, 1947, ten days later than her date of admission.

In her delirious state, the patient was complaining intermittently of lower abdominal pain not coincidental with uterine contraction. The globular abdomen was unduly prominent, giving one the impression of a giant child, multiple pregnancy, or polyhydramnios. Palpation of the abdomen was quite painful to the patient and revealed a single large fetus in the transverse plane with a large prominent head in the right lower quadrant at the pelvic brim. Fetal movements were dubious and heart sounds could not be elicited. Rectal examination revealed a parous, nondilated, only slightly softened cervix. Considering prolonged labor with exhaustion due to fetopelvic disproportion from a monstrosity or giant child as a likely diagnosis, a flat plate of the abdomen was taken.

A wet reading of the plate revealed a single uterine pregnancy with the body in a transverse lie possessed of an unusually large head measuring approximately 15.2 cm. in its occipitofrontal diameter. A final reading, not available preoperatively, stated that the apparent enlargement of the head was caused by undue distortion. Furthermore, the outline of the uterus could not be demonstrated but the pelvic inlet appeared relatively small.

Blood pressure was 130/80, pulse rate 120, temperature 100.6° F., and respiration 26.

Clinical impressions at this time were as follows: Fetopelvic disproportion; giant or hydrocephalic fetus; transverse presentation with no cervical dilatation; maternal exhaustion with low-grade fever following fourteen hours of labor without obvious progress. Consensus of opinion now favored abdominal delivery, if the patient's general condition could be sufficiently improved following the administration of fluids, blood, sedation and antibiotics. Three hours later she was considered a fair risk for cesarean section under Nembutal and local anesthesia.

When the abdomen had been opened in the midline, there presented a smooth, congested surface, below which the fetal parts could be palpated with ease. Suspicions as to the nature of this sac were confirmed when the bladder flap could not be identified prior to performance of a low segment operation. The uterus, found to be only slightly enlarged and softened, was pushed forward and downward by this abdominal mass. The possibility of an extra-uterine pregnancy now became a fact.

In the process of separating the mass from the inferior surface of the liver, the parietal peritoneum, and contiguous loops of intestines to which it was firmly adherent, the wall

was inadvertently ruptured, releasing under pressure a moderate amount of dark brown amniotic fluid. Suction was applied and the opening was extended to deliver a large, normally developed, live, male fetus weighing 9 pounds, 5½ ounces, and measuring 51.25 cm. in length. The infant breathed spontaneously and its condition remained good throughout the hospital period.

The placenta was attached to the inferior and inner aspect of the sac wall and was the site of a moderate amount of bleeding which made its immediate removal necessary. Closer inspection of this gestation sac revealed it to be the left tube with the isthmal portion readily identifiable. The ampullary and infundibular portions were widely dilated. The operation consisted further in removal of the left tube, peritonealization of rough surfaces, sprinkling of 5 Gm. of sulfanilamide powder over the operative site, and a quick abdominal closure in layers as the patient's condition was never better than fair. Her postoperative course was uneventful. Both mother and infant were discharged in good condition on the eleventh day after operation.

Pathological Report

Macroscopic.—"Received partially immersed in formalin fixative are two specimens. One is a bi-lobed placenta, with a 57 cm. length of umbilical cord attached to the larger lobe, which measures 13 by 9 by 6 cm. in maximum diameters. There is an isthmus measuring 5 by 5 by 2.5 cm. connecting this to the other lobe which measures 12 by 9 by 8 cm. The other specimen is a wrinkled, partially translucent, and pouch-like membrane varying from 1 mm. to 1 cm. in thickness. The thinner part presents relatively smooth inner and outer surfaces and areas where it can be split into two layers; the thicker part of the membrane has a relatively smooth outer surface but the inner surface is roughened by hemorrhagic and grayish strands. This thicker part of the specimen has an area of approximately 17 by 9 cm., while that of the thinner part is about 17 by 20 cm. No ovarian tissue or tubal tissue is recognized as such, except for the lumen of the attached isthmal portion of the tube opening into the cavity of this sac-like structure."



Fig. 1

Microscopic.—"Section 1 reveals cross-section of the isthmus of the fallopian tube with a wall of hypertrophied smooth muscle fibers, abundant vascularization, and an increased amount of fibrous tissue." (Fig. 1.)

"Section 2 is from the thicker part of the fetal sac having a relatively smooth surface covered by fibrin, a wall consisting of smooth muscle fibers and connective tissue, and a lining which includes placental tissue and exudate showing varying degrees of necrosis and lysis." (Fig. 2.)



Fig. 2.

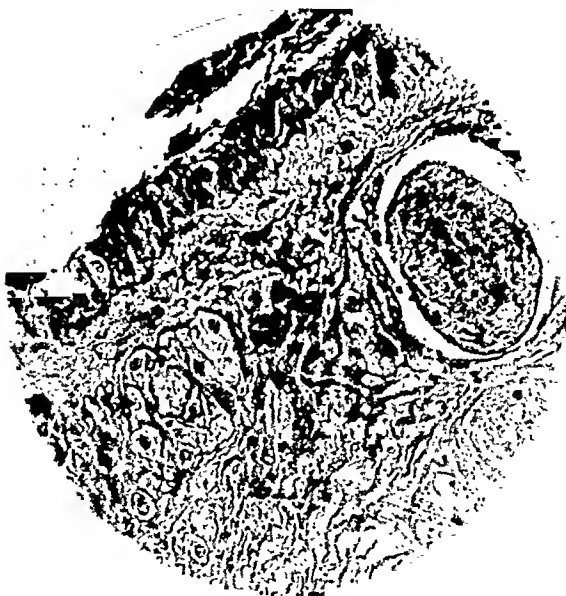


Fig. 3.

"Section 3 is from the thinner part of the saclike structure, the inner surface of which presents columnar epithelium (tubal) overlying decidual cells, fibrinous exudate, necrotic tissue, and a chorionic villus." (Fig. 3.)

Impression.—"Tubal pregnancy at term."

Although one of these cases of intraepithelial carcinoma (Case 4) was discovered one year prior to the others in this series, two cases (3 and 5), discovered in a total of 110 routine biopsies, represent an incidence of 1.8 per cent. Although the series is admittedly too small to be of statistical value, this high incidence was so surprising to us that we thought comparison of our small series with published reports might be of interest from the standpoint of management of these cases.

Our incidence compares favorably with Sehiller's finding of 1.41 per cent "incipient carcinomata" in serial sections of cervixes from 425 panhysterectomies,² and TeLinde and Galvin's incidence of 1.3 per cent from biopsy material. The incidence of very early invasive carcinoma (2 cases in 110 biopsies) in our series is even higher than the findings of TeLinde and Galvin¹ (2 cases in 240 total hysterectomies).

We felt that our finding of this high incidence of intraepithelial carcinoma and early invasive carcinoma in this series of 110 routine biopsies might be due to the management of most of the cases. We hypothesized that the routine use of rebiopsy and scalpel conization of the cervix with complete microscopic study of the excised tissue, in those cases where an equivocal lesion was present in the original biopsy, might give as complete information as ablation of the cervix or total hysterectomy. That this hypothesis might be correct seemed further substantiated by the findings of Stevenson and Seipiadis.³ In a review of all of the cervical tissue in the files of the Gynecological Pathology Laboratory of the Johns Hopkins Hospital, these authors did not have the patient at hand for additional tissue for study, and their incidence of intraepithelial carcinoma was roughly 0.45 per cent (18 in some 4,000 cases studied).

The incidence of intraepithelial and early invasive carcinoma in our series was roughly comparable to published statistics in routine hysterectomies where the entire cervix was immediately available for study. It was roughly three times the incidence reported in a series where additional tissue was not available for study. These comparisons have led us to believe that if the cervix were available for study in all cases where equivocal lesions are discovered in routine biopsy, a far greater number of intraepithelial and early invasive carcinomata would be discovered than has heretofore been possible.

Conization of the cervix as a diagnostic method in these cases has been considered favorably by TeLinde and Galvin.¹ Combined with low amputation, utilizing the Sturmdorf flap principle, it is the preferred treatment by Martzloff when "carcinomatoid change" is found in the original biopsy.⁴ It seems to us that the method of attempting to get a more complete picture of the cervical lesion by scalpel conization might have sufficed as treatment in the two cases in which total hysterectomy was done and no carcinoma, either intraepithelial or invasive, was found in the excised cervix (Cases 3 and 5). In the one case where total hysterectomy revealed early invasive carcinoma (Case 6), scalpel conization would have revealed the lesion, and the cervix and uterus could have been utilized for the local application of radium. Case 4 might either have shown no additional invasive lesion, sparing the patient unnecessary irradiation, or invasive carcinoma might have been found as in Case 7, justifying the irradiation therapy prescribed.

As the result of the study of this small series of cases, we feel that our concepts of cervical biopsy have changed. In the future we will consider biopsy as a screening process in those cervixes that present no grossly recognizable cancer. Cauterization of the cervix at the time of the original biopsy will be abandoned so that additional tissue for study will be available if necessary. The finding of equivocal lesions, atypical metaplasia and possible intraepithelial

PREGNANCY COMPLICATED BY SUBARACHNOID HEMORRHAGE

A Report of Three Cases

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SUBARACHNOID hemorrhage has been established as a definite, relatively common clinical entity in the past sixty years. It rarely occurs, however, as a complication of pregnancy, labor, or the puerperium. Moskowitz and Schneider, in 1938, reported three cases occurring during labor. They found thirteen cases reported up to that date. A recent search of the literature revealed only four additional occurrences: one reported in 1938 by Pancot and Galle, secondary to an intracerebral accident due to syphilis; and three reported by T. Dahle in 1946, in which toxemia of pregnancy was considered the causative factor.

In the general consideration of subarachnoid hemorrhage, aside from its occurrence as a complication of pregnancy, a variety of diseases and conditions has been suggested as etiologic factors. Infections such as influenza, typhoid, smallpox, and syphilis; toxic conditions including alcoholism, lead poisoning, and toxemias of pregnancy; and vascular lesions like arteriosclerosis and aneurysms have all been considered. The latter have been found most frequently. Two types of subarachnoid hemorrhage are distinguished: primary and secondary. In the first, the bleeding is into the subarachnoid space from a ruptured adjacent artery. This type is characterized by headache, delayed loss of consciousness, and late signs of paralysis. In the second type the bleeding is due to extension of intracerebral hemorrhage into the subarachnoid space, and is characterized by early signs of paralysis and rapid loss of consciousness. The latter occurs more often in the older age groups, and is usually on an arteriosclerotic basis. In the primary type the younger age groups are more commonly affected, and the cause is thought to be a rupture of a small "berry" type congenital aneurysm. Such aneurysms are frequently found at routine autopsies in which the incidence is reported to be 0.3 to 1.0 per cent. Congenital aneurysms result from a local weakness or defect in the media of the cerebral arteries and occur at the points of bifurcation in the region of the Circle of Willis where the vessels are essentially suspended in fluid with little external support. These vessels may rupture easily under the impact of trauma from emotional strain, increased systolic pressure, or physical exertion.

In the initial phase of the accident the striking symptoms of headache, vomiting, bradycardia, followed by stupor and coma, manifest themselves. If the patient does not succumb shortly after the accident the condition progresses with signs of meningeal irritation such as pain in the head, rigidity of the neck, a positive Kernig's sign, leucocytosis and fever. The pathognomonic sign of subarachnoid hemorrhage is the finding of bloody spinal fluid under increased pressure.

Case Reports

CASE 1.—I. R. T., a 26-year-old Negro para 0, gravida ii, in her eighth month of gestation, was admitted to the hospital on Sept. 10, 1946, with painless vaginal bleeding of about ten hours' duration. At the time of the onset of the vaginal bleeding she complained of nausea, vomiting, and severe frontal and occipital headache, throbbing in character. The past history was essentially negative except for a spontaneous three-month miscarriage in 1945. Her blood pressure was essentially negative. The uterus was enlarged to almost the size of a term pregnancy, and the fetal heart tones were heard. A catheterized urine specimen revealed a two plus albumin and hyaline casts. An x-ray examination of the abdomen with air insufflation of the bladder demonstrated a shadow suggestive of a low implantation of the placenta on the left posterior aspect of the uterus. A tentative diagnosis of partial placenta previa and toxemia of pregnancy was made, and it was decided to deliver the patient

Comment

The literature is replete with the possible termination of tubal pregnancy but we were not able to find one reference to the salvaging of a live full-term fetus from an unruptured uterine tube.

Lichtenstein¹ called attention to the fact that, when the placenta develops toward the mesosalpinx, the pregnancy is more likely to continue. In 90 per cent of advanced tubal pregnancies, this "basiotrope" implantation is found.

To this postulation, we offer as an additional possibility, a luminal implantation site into the connective tissue stroma of the numerous and elongated mucosal folds in the ampullary portion of the tube, permitting little or no encroachment upon the tubal wall by the trophoblastic villi—a phenomenon not possible in a mural or luminomural implantation site.

Appreciation is acknowledged for the cooperation of the Pathology Department of Howard University Medical School.

Reference

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The laboratory findings were, at no time remarkable. She had a moderate leucocytosis ranging from 9,100 to 11,550, but red counts, bleeding, and clotting times, prothrombin indices, blood chemistries, and serologies were all normal. Spinal fluid chemistries due to the admixture of blood were not reliable, and spinal fluid cultures, which revealed nothing on direct smear, showed a slight growth of gram positive cocci believed to be a contaminant.

While the diagnosis in this case was relatively easy and definite, the treatment and management were uncertain. The main problem was the selection of the propitious time for the termination of pregnancy in view of the danger of precipitating another and perhaps fatal hemorrhage. Her apparently moribund state, however, forced the issue with, fortunately, a satisfactory outcome.

CASE 3.—W. W., a 24-year-old white primiparous female, was admitted to the hospital on June 19, 1947, in active labor at term. Examination showed that she was almost ready for delivery. Under general anesthesia a term male infant was delivered with low forceps at 7:30 P.M. Following delivery a tendency toward postpartum bleeding was noted and the patient received an ampule of infundin intramuscularly, an ampule of ergotrate, and a cubic centimeter of pitocin intravenously in the course of some twenty minutes. At 8:15 P.M. she reacted from her anesthesia, became quite restless, and was given $\frac{1}{4}$ grain morphine. The following day the patient appeared drowsy, but that was attributed to the effect of the anesthesia. On June 21, 1947, she complained of a marked headache. The next day the headache became more severe, and she had a stiffness of her neck with no apparent other signs. A spinal puncture was done and uniformly bloody fluid obtained with an initial pressure of 360 mm. of water, which on withdrawal of the fluid came down to 210 mm. By June 23 her temperature rose to 102° F., she became markedly lethargic, and complained of severe frontal and occipital headache. Examination disclosed marked nuchal rigidity, a positive Babinski, and resistance to straight leg raising, but her pupils and fundi remained normal. The blood pressure was 120/70 and the pulse rate fifty. The following day another spinal puncture again showed a grossly bloody fluid and an initial pressure of 332 mm. of water which was reduced to 162 mm. by withdrawal of fluid. She was treated expectantly with absolute bed rest and became more alert, her headaches gradually subsided, the pulse rate rose to seventy, and her nuchal rigidity and pathologic reflexes disappeared. She was allowed to be up July 2, and was discharged from the hospital the following day with no apparent residual signs. The laboratory findings were not remarkable. She ran a leucocytosis of from 11,100 to 14,050 with 86 per cent polymorphonuclears. Hemoglobins, red counts, blood chemistries, and serology were normal. Spinal fluid examinations were grossly bloody and showed positive Pandys and high cell counts.

This case is of interest in that it exemplifies the dangers inherent in the liberal use of oxytocics, because such drugs may give rise to just enough pressor action to precipitate rupture of a congenital aneurysm with resulting subarachnoid hemorrhage.

Discussion

The cases here presented are all proved examples of subarachnoid hemorrhage complicating pregnancy, labor, and the puerperium. All occurred in young women of 24 and 26 years of age. Since none showed either early coma or residual paralysis they were probably of the primary variety and most likely secondary to congenital aneurysms of the Circle of Willis. Two of our cases presented similar patterns including normal blood pressures, moderate elevations of temperature, moderate leucocytosis, grossly bloody spinal fluid with markedly increased pressure, and meningeal signs such as nuchal rigidity and pathologic reflexes several days following the original accident. The third case differed from the others in that the blood pressure was moderately elevated and the spinal fluid pressure was not unduly high. In two of our cases, as in those reported by Moskowitz and Schneider, toxemia was not a factor; but in one, as in the three cases reported by T. Dahle from Norway, toxemia may have played a role in the etiology. The diagnosis of subarachnoid hemorrhage complicating pregnancy and delivery may be obscured by other conditions such as shock, anesthesia, and a pre-eclampsia. Dahle and others have emphasized the latter possibility and have pointed out that

by cesarean section. Lumbar puncture for spinal anesthesia showed a uniformly bloody spinal fluid, but its significance was overlooked. A low cervical section was done and a premature viable male infant delivered. For three days postoperatively she ran a temperature of 100.5° F. She continued to complain of headache, but this was considered to be due to spinal anesthesia. On Sept. 16, 1946, her temperature rose to 102° F. She complained of severe headache and nuchal rigidity, but there was no nausea or vomiting. Examination on that date revealed no eye signs or pathologic reflexes, but definite evidence of meningeal irritation developed gradually in the form of a fine nystagmus, marked nuchal rigidity, absent upper reflexes, depressed lower reflexes, and a positive Kernig's sign. A lumbar puncture on Sept. 20, 1946, revealed a grossly bloody fluid with an initial pressure of only 190 mm. of water and a four plus Pandy. The headache and nuchal rigidity gradually subsided. Spinal puncture on September 21 and September 23 demonstrated a gradual return to normal with the fluid on the latter date showing a xanthochromic color and only an occasional red blood cell and a one plus Pandy. The patient had a clear sensorium and was discharged from the hospital on Sept. 27, 1946, in good condition. The laboratory findings during her stay at the hospital were not remarkable. The urine which on admission had shown a two plus albumin became negative. On September 16 the white count rose to 10,650, but at other times was within normal range. Blood chemistry and serology were normal. A spinal fluid culture on September 21 showed no growth.

In this case the accident, in all probability, occurred prior to her cesarean section as evidenced by her symptoms on admission and the bloody spinal fluid obtained at that time. It was overlooked due to the existence of a toxemia.

CASE 2.—D. R., a 26-year-old white multipara, was admitted to the hospital on Nov. 20, 1946, in her thirty-fourth week of gestation, with a complaint of severe headache. Nine hours prior to admission the patient bent over and suddenly experienced a terrific pounding in the frontal region which subsequently became generalized and progressively more severe. She felt faint, did not lose consciousness, and within one and one-half hours developed marked nausea and projectile vomiting. Her family and past history was negative. She had had one child and one abortion. She did not appear acutely ill. The blood pressure on admission was 110/70; the pulse rate 66. Her pupils reacted to light and accommodation and the right fundus showed evidence of papilledema. There was moderate nuchal rigidity, but no pathologic reflexes were present. A spinal puncture revealed a uniformly bloody fluid with an initial pressure of 280 mm. of water which dropped to 180 mm. upon slow withdrawal of the fluid. She was maintained at absolute bed rest, but in spite of that she apparently had a second episode of bleeding with an exacerbation of the headache. Examination at this time revealed well-established bilateral papilledema and absent patellar reflexes. Spinal puncture showed a xanthochromic fluid with pressures identical with those of the tap on admission. During the next several days, except for dizziness on movement of her head, the patient showed signs of improvement. She was allowed to be up on December 12, and the following day was found sprawled unconscious on the floor. Her breathing was stertorous. She vomited and urinated involuntarily. All superficial and deep reflexes were hyperactive; and bilateral positive Babinski and ankle clonus were present. She gradually became excited and incoherent. Her temperature for the first time rose to 100° F. A spinal puncture the following day again showed a grossly bloody fluid with an initial pressure of 560 mm. of water which was reduced to 260 mm. by withdrawal of fluid. On December 15 the patient appeared to be moribund. In view of the fact that the baby was viable, and that the additional trauma of labor was undesirable, it was decided to terminate the pregnancy by section before term. The lumbar puncture for spinal anesthesia still revealed a bloody fluid and an initial pressure of 450 mm. of water. A classical section was done, and a 7-pound viable female infant delivered. The patient regained consciousness promptly after the operation, and her improvement was uninterrupted and progressive. In a period of seven days spinal fluid pressure dropped from 600 mm. to 300 mm. of water. She showed evidence of encephalopathy simulating schizophrenia. But within a week she manifested marked improvement, showed a return of considerable alertness, and was discharged from the hospital on Jan. 7, 1947, in good condition.

KIDNEY FUNCTION IN THE FETUS

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THE function of the vital systems of the fetus during intrauterine life has been discussed to a very limited extent in our textbooks in the past. This material is neither within the scope of the embryology textbook nor the physiology textbook. The treatment of a premature infant and also an evaluation of its prognosis are based on a knowledge of the physiology of the fetus. Evidences of the onset and extent of activity of the various organs come, for the most part, from indirect findings, but occasionally some direct evidence presents itself. This case is reported because it gives some indication of the quantity of urine excreted during fetal life, as proved by the enormous distention of the bladder with urine at the time of delivery.

Case Report

Mrs. R. B., aged 23 years, gravida iii, para ii, was admitted to St. Elizabeth Hospital June 17, 1947. Expected date of delivery was July 21, 1947. The first two children had no physical anomalies. The patient had made two prenatal visits to her physician: the last visit was the day before hospital admission and the first visit four weeks previously. Physical examination, pelvic measurements, and routine laboratory findings were essentially negative at the first visit. In the interval of four weeks between the two visits, the patient gained 13¼ pounds, blood pressure became elevated to 148/90, there was 2 plus edema of the feet and ankles and a trace of albumin. There was a very marked increase in the size of the abdomen, arousing suspicion of hydramnios.

The first stage of labor progressed normally. In the second stage of labor, the head descended and was delivered spontaneously, but after delivery of the anterior shoulder further descent stopped completely. On pelvic examination, it was ascertained that a greatly distended fetal abdomen prevented any further progress. Under manual guidance, the fetal abdomen was incised, with evisceration contemplated. However, on entering the abdominal cavity, there was escape of straw-colored fluid. After drainage of 3,800 c.c. fluid, the delivery was completed; 400 c.c. fluid remained in the bladder, making a total of 4,200 c.c. measured urine drained from the bladder. Fig. 1 demonstrates the size of the distended abdomen.

An autopsy was obtained on the infant. The positive findings were confined to the greatly distended abdomen with the dilated bladder. The external genitals were essentially negative. The bladder wall was extremely thin and the lining showed crusting and calcified deposits. The ureteral orifices were located with difficulty and the ureters showed a saccular dilatation. The ureters led upward into relatively normal-sized kidneys which showed only moderate hydronephrosis on cut surface. The cut surface of the left renal parenchyma showed definite fibrous and inflammatory changes. Careful examination of the lower urinary tract revealed a patulous internal sphincter leading into a dilated distorted posterior urethra. A probe could be passed through the entire length of the urethra. It was noticed that there was an elongation of the posterior urethra. Gross appearance of the organs is shown in Fig. 2. Explanation of the obstruction has three possibilities: 1. A thin membrane ruptured by the probe but not noted. 2. A redundant fold of mucosa from the elongated urethra forming a mechanical obstruction over the orifice of the urethra. 3. An adynamic type of obstruction might have played a part initially, but unlikely in the absence of any central nervous system disease.

without recourse to spinal puncture a mistaken diagnosis may be made. Still another factor which may obscure the diagnosis is delivery under spinal anesthesia, since the manifestations of "spinal headache," nuchal signs, and meningismus are frequently encountered following that type of anesthesia. In spite of the fact that lumbar puncture in the face of an increased intracranial pressure is considered by many as a dangerous procedure, all of these cases were subjected to repeated punctures. Removal of the irritating bloody fluids and lowering of the intracranial pressure apparently served to decrease the meningeal irritation and lessen the lethargy. The taps were done cautiously, the fluid removed slowly; and in the cases with increased pressure, the pressure was decreased by not more than half. The delivery of Case 2 by cesarean section was in accord with the conclusion of Moskowitz and Schneider that when the diagnosis has been established, cesarean section offers the least additional trauma. The emptying of the uterus in this case seems to have been a factor in her recovery. It is quite possible that cesarean section by decreasing abdominal pressure and allowing for stagnation in a dilated splanchnic vascular bed decreases the circulating blood volume, the venous pressure, and hence the intracranial pressure.

Summary

1. Three cases of proved subarachnoid hemorrhage complicating pregnancy have been reported.

2. All three were apparently of the primary type and probably occurred at the sites of congenital aneurysms of the Circle of Willis.

3. Oxytocics should be used cautiously, particularly in cases with elevated blood pressure, a history of migraine, or any suggestive premonitory signs.

4. The use of repeated spinal puncture to relieve the symptoms of intracranial pressure and the employment of cesarean section to avoid the trauma of labor proved efficacious in the cases reported.

5. Subarachnoid bleeding may occur in milder forms, and be obscured by general anesthesia, shock, toxemia, or symptoms of "spinal headache."

6. The more frequent employment of diagnostic lumbar puncture would obviate those sources of error since the finding of bloody spinal fluid under increased pressure is pathognomonic of subarachnoid hemorrhage.

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hyaline changes have progressed to the point of actual calcific deposits on the surface of the bladder. While there is no bacterial clump, definite chronic inflammatory changes are present. In the region of the prostatic urethra, marked fibrous inflammatory changes are present, with some focal calcific deposits. The changes in the bladder are almost certain to be secondary to obstruction with overdistention, but those in the posterior urethra may be more primary than was apparent on the gross studies.

Summary of Anatomic Findings:—

1. Massive dilation of urinary bladder.
2. Compression of abdominal and thoracic viscera by distended urinary bladder.
3. Bilateral hydroureter.
4. Early hydronephrosis with pyelonephritis.

Fetal Kidney Function

The kidneys are functioning at birth and one frequently observes urination within a very short time after the birth of an infant. Knowing that the infant is often born with a full bladder, we can only speculate on how frequently the fetus urinates during the last months of intrauterine life and in what quantities urine is excreted.

Authorities are in agreement that urinary excretion begins at the fetal age of about three months. Excretion is scant and continues at a retarded rate because the fetus is not dependent on this avenue of elimination. Removal of waste products from the fetus rests upon the placental circulation.

Specific evidence concerning the quantity of urine secreted is best observed in obstructive lesions where the urine is retained. In cystic kidneys, the secretory portion of the uriniferous tubules has failed to unite with the collecting portion of the tubules. Urine is secreted but it is retained in these blind tubules. Such kidneys may enlarge to huge proportions and be the cause of a serious dystocia in the second stage of labor. The case of the infant reported is of a different nature, the child having a normally developed upper urinary tract but an obstruction preventing escape of urine from the bladder. This infant having normal kidneys should be representative of normal fetal physiology. A fetus with a polycystic kidney has a developmental defect of the kidney itself, and this probably does not represent normal function.

In a normal fetus, there are several possibilities in the disposal of the urine that finds its way to the bladder. In early fetal development, the cloaca becomes divided into two parts by the urorectal fold. The ventral portion becomes the urinary bladder and the dorsal portion becomes the rectum. When this septum forms, the cloaca is a blind pouch, but soon the cloacal membrane ruptures, establishing the urogenital and anal orifices. Urine excreted after the establishment of the urogenital orifice may then be voided into the amniotic fluid. In the opinion of most authorities, the fetus drinks amniotic fluid and thus keeps the volume of the fluid within normal limits. It is possible that our case may have had a thin persistent urethral membrane which was ruptured by probing, but was not noted on gross examination.

Another possible means of disposal of urine from the fetal bladder is by reabsorption. The allantois which later is a portion of the urinary bladder develops a rich plexus of vessels in its walls at an early age. This plexus of arterics and veins connects directly with the main circulatory channels of the embryo and may, for at least certain periods, absorb urine from the bladder. The allantoic stalk eventually becomes reduced to the urachus toward the direction of the umbilicus. At times an umbilicourinary fistula may persist at birth.

In summarizing, this infant had a greatly distended bladder containing 4,200 c.c. urine. The kidneys were essentially normal except for secondary changes due to secreting against pressure. The volume of urine found in the bladder of this infant may be a clue to the approximate amount secreted by all fetuses during the last months of intrauterine life.

Microscopic Findings:—Kidneys: sections of the kidneys show definite evidence of obstructive renal disease. In some areas, the glomeruli are quite normally formed, but throughout there is some increased cellularity and congestion. In focal areas, complete



Fig. 1.—Bladder refilled with fluid after delivery, demonstrating the abdominal distention which obstructed vaginal delivery.



Fig. 2.—Cut surface of bladder, ureters, and kidneys.

atrophy of glomeruli structures with associated tubules is encountered. It would appear that the renal changes are secondary to a long-standing obstruction rather than playing a part in its cause.

Urinary Bladder and Urethra:—Sections of the urinary bladder show a marked thinning of the bladder wall with fibrous and hyaline changes in the wall and mucosa. The

A biopsy taken from the cervical ulceration was reported as a subacute cervicitis. Donovan bodies were detected in tissue taken from the edge of the ulceration. Under Fuadin therapy, the process healed completely.

CASE 2.—M. K., a 34-year-old Negro widow, para ii, gravida ii, was admitted, complaining of vaginal bleeding and cramps for two weeks prior to admission. Menses were normal until 14 weeks ago, at which time the patient had her last regular menstrual period. Vaginal bleeding started two weeks prior to admission: amounts varied and were at times profuse. Attempted induction of abortion was denied.

Physical examination on admission revealed an acutely ill Negro woman with a temperature of 101.4° F. and pulse 120. The general examination was not remarkable. The lower half of the abdomen was moderately distended with no palpable masses. Pelvic examination revealed an enormously enlarged cervix which was moderately soft and bled profusely on touch. The uterus was not completely outlined, due to extensive parametrial induration. Speculum examination showed the cervix filling the entire vault of the vagina and covered by an exuberant polypoid ulcerative process from which free bleeding occurred. There was no rectal involvement.

The admission diagnosis was carcinoma of the cervix and abortion, probably complete. The biopsy report showed acute and chronic cervicitis with no evidence of malignancy. Serologic tests for syphilis revealed strongly positive reactions. Dark-field examinations were negative. The Frei test was strongly positive. Examination of material obtained by biopsy and stained with Wright's stain revealed the presence of Donovan bodies.

Under Fuadin therapy and several exposures of x-rays delivered by a vaginal cone, there was some improvement, but considerable ulceration still persisted. Streptomycin, 1 Gm. four times daily for five days, brought about a marked improvement. At the time of discharge, there was still a 1 cm. area of ulceration on the posterior lip of the cervix, the entire cervix was much smaller in size, and, while still moderately fixed, was much more mobile than on admission. Considerable parametrial induration remained on the left side. When she was observed later in the Out-Patient Department there was a moderate amount of residual parametritis but the cervix appeared completely healed and menstrual periods were normal.

CASE 3.—E. F., a 35-year-old, married, Negro woman, para iii, gravida iii, was admitted with the chief complaints of leucorrhea of twelve months duration and intermittent vaginal bleeding of five months duration.

Five years prior to admission she had been treated for syphilis. Three years previously a posterior colpotomy had been performed at another institution. About one year before the present admission, the patient had been cystoscoped because of hematuria and a right hydronephrosis was found but no etiological factor for this condition was given in the hospital report. Two months prior to her present admission, the patient was seen at an institution where a tentative diagnosis of carcinoma of the cervix was made pending the report of a biopsy which, however, indicated simply a marked chronic inflammation.

Examination on admission to Bellevue Hospital revealed nothing essentially abnormal except for the gynecologic findings. There was a good parous pelvic floor. The cervix was markedly enlarged and indurated, and on the surface could be felt many firm, irregular nodules. The posterior vaginal wall behind the cervix was adherent to underlying scar tissue, probably the result of the previous colpotomy. The uterus was apparently normal in size with considerable parametrial thickening, particularly on the right side. The adnexa could not be distinguished. Speculum examination showed the entire surface of the portio-vaginalis replaced by an extensive granular ulceration with a nodular surface which bled readily. A tentative diagnosis of carcinoma of the cervix was made, and a biopsy performed, which showed a subacute and chronic cervicitis but no evidence of malignancy. The Frei test was positive and the Wassermann was reported several times as anticomplementary. A biopsy revealed the presence of Donovan bodies. The patient was given Fuadin, 5 c.c. three times weekly. After a three weeks' course of this medication, the ulceration was almost completely healed.

FOUR CASES OF GRANULOMA INGUINALE OF CERVIX DIAGNOSED CLINICALLY AS CARCINOMA*

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IN THE woman, granuloma inguinale produces an ulcerative lesion which most frequently involves the inguinal region and external genitals. Other areas, however, may be involved. When the disease attacks the cervix, it bears a striking resemblance to carcinoma but, fortunately, offers a vastly better prognosis. The gross appearance of the ulceration may vary from a simple, raised, granular lesion to a distinctly polypoid and fungating one. It may be soft or indurated and, though extensive, is always sharply circumscribed. The process may involve the deeper tissues, producing extensive parametrial induration with a resulting frozen pelvis. Bleeding is frequently provoked by trauma and the patient may complain of irregular vaginal bleeding and discharge. Like carcinoma, it spreads by direct extension as well as by lymphatics. In addition, cases of distant osseous involvement have also been reported.^{1, 2, 3} While a hematogenous spread had been considered likely, only recently has this been conclusively proved by Paeker, Turner, and Dulaney⁴ who have succeeded in demonstrating the presence, in blood cultures, of an organism having the morphologic appearance of Donovan bodies.

The diagnosis of granuloma inguinale can be established by finding the Donovan bodies in the pathognomonic cell, a large mononuclear cell with a foamy cytoplasm. Material can be obtained with a curette or biopsy punch, preferably from the expanding border of the ulceration, and stained with the Wright, Giemsa, Dieterle or Mortara stain.

CASE 1.—B. S., a 17-year-old Negro single girl, para i, gravida i, was admitted with the chief complaints of lower abdominal pain and vaginal bleeding. On a previous admission, she had been treated for an acute salpingitis, cervicitis, and urethritis. Menstruation had always been completely irregular and for the past year there had been considerable dysmenorrhea. Three days after the onset of the present episode of vaginal bleeding, the patient developed sharp intermittent lower abdominal pain.

On admission, there was tenderness in both lower quadrants with considerable voluntary spasm. Vaginal examination revealed a two-finger introitus with excellent perineal support. The cervix was anterior, conical, and closed. On the anterior lip was a palpable irregularity which felt not unlike another external os. The uterus was normal in size, and retrodisplaced with limited mobility. The adnexa were thickened, prolapsed, and somewhat tender. On rectovaginal examination, there was some tender induration high up in the cul-de-sac. Speculum examination revealed a 1½ to 2 cm. red, granular ulceration on the anterior lip and a smaller one on the posterior lip of the cervix. The borders were raised and bleeding was readily provoked on manipulation, simulating a friable carcinoma. While under observation the entire ulceration became more exuberant.

The admission temperature was 101° F. and pulse 108. Serologic tests for syphilis were negative. Dark-field examination of serum obtained from the ulceration was negative. The Frei test was positive.

*Presented at a meeting of the New York Obstetrical Society, Feb. 10, 1948.

carcinomata will be followed routinely by a complete sectioning of the original block and wide conization of the cervix. As emphasized by TeLinde and Galvin,¹ the preparation of the tissues will be by the best possible methods, and frozen sections will not be utilized. Conization will be performed with the scalpel rather than the cautery, so as not to desiccate the specimen. A registry of intraepithelial carcinomata of the cervix has been proposed to be sponsored by the local Obstetrical and Gynecological Society. The purpose of this registry will be the confirmation of diagnoses by competent gynecologic histopathologists, and the provision for adequate follow-up of these cases.

It is felt that in the study of a lesion in which the highest order of opinion with respect to its true nature is still divided, concerted action by a group of gynecologists and pathologists will progress faster than individuals working alone.

CASE 1.—Aged 18 years, para 0, gravida i. Irregular vaginal bleeding three and one-half months. Never any cramps.

Uterus enlarged the size of a three and one-half months' pregnancy, cervix markedly hypertrophied, large raised circumoral erosion hyperemic and covered with mucopurulent exudate and bled easily to touch in all areas.

Biopsy report: "Cervical granuloma showing decidual reaction with acute and chronic inflammation" (Fig. 1).

Consultant (pathologist) unwilling to state that epithelial lesion was not carcinoma. Another biopsy recommended.

New biopsy performed, a total of five times in a period of four weeks. All sections showed metaplasia with decidual reaction and a disappearance of the inflammatory reaction following penicillin therapy. The cervix was not cauterized, pregnancy continued to normal term delivery, at which time cervical biopsy disclosed decidual reaction.

CASE 2.—Aged 19 years, para i, gravida ii. Curettage for continued bleeding following spontaneous abortion at two and one-half months. Cervix showed no gross lesion.

Diagnosis of material removed with dull curet: "Chronic cystic endocervicitis with squamous cell metaplasia." Rebiopsy requested.

Six weeks following original curettement and because of the equivocal nature of the marked metaplasia seen in the original curettement, scalpel conization performed. Cervix showed no gross lesion.

Biopsy report: "Cervix showing squamous cell metaplasia" (Fig. 2).

CASE 3.—Aged 23 years, para iv, gravida iv. Abdominal pain intermittent for two years, worse for one month. Profuse leucorrhea for several years. No metrorrhagia. Last menstrual period three weeks prior to biopsy.

Uterus anterior and normal size, bilateral adnexal tenderness. Cervix was the site of an extensive circumoral erosion which bled in all areas.

Biopsy report: "Chronic cervicitis with squamous cell metaplasia."

Because of the extensive nature of the erosion and its vascularity, rebiopsy done three days later and adjacent to the previous biopsy.

Biopsy report: "Intraepithelia carcinoma" (Figs. 3A and 3B). Consultant (pathologist) agreed.

Total hysterectomy with conservation of both tubes and ovaries. Histological section of multiple blocks of the excised cervix failed to reveal any additional foci of intraepithelial carcinoma or invasive carcinoma.

CASE 4.—L. P., a 23-year-old, single, Negro woman, para i, gravida i, was admitted with the chief complaints of irregular vaginal bleeding, discharge, and bilateral lower abdominal pain. For several weeks prior to admission, she was attending a cancer clinic, where a tentative diagnosis of carcinoma of the cervix was made. Repeated biopsies were taken and all were reported as showing evidences of a granulomatous inflammatory process. Since no treatment was offered at this clinic, the patient came to Bellevue Hospital. At the time of admission the general examination was essentially negative. Pelvic examination revealed a two-finger introitus, with a large fungating mass replacing the cervix and filling the entire vault of the vagina. The fundus was small, and seemed to be fixed anteriorly. On the posterior vaginal wall, about 1½ inches from the introitus, was a raised ulceration which extended upwards to involve the entire posterior and lateral walls of the vagina. The process had a raised, irregular edge, was comparatively soft but friable, and bled readily. There was extensive rectovaginal septum induration as well as bilateral stony-hard parametrial involvement.

The Wassermann test was 4 plus and the Frei test was negative. Examination of tissue stained with the Wright and Mortara stains revealed Donovan bodies. The patient was given Fuadin, 5 c.c. intramuscularly three times weekly, and some x-ray therapy. After a month of this regime considerable improvement was noted. The posterior and lateral vaginal walls were completely healed. The cervix could be readily identified and showed patchy areas of epithelialization although the parametrial induration persisted. Subsequently, the cervix healed completely but considerable residual induration of the parametrium was still noted after several months.

Summary

Four cases of granuloma inguinale of the cervix have been reported. They illustrate the marked similarity between this process and carcinoma, in that patients complain of vaginal discharge, irregular bleeding, and perhaps lower abdominal pain, while examination reveals ulceration of the cervix which bleeds readily on manipulation. Frequently there is extensive parametrial induration as well. However, examination of suitably stained material, preferably from the edge of the ulceration, discloses the identity of this process. Granuloma inguinale is characterized by the presence of a chronic inflammatory process with a pathognomonic cell containing Donovan bodies.

In all cases where carcinoma of the cervix is suspected clinically, but is not confirmed by histologic study, properly stained material should be examined for the presence of the "granuloma" cell and its Donovan bodies.

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UNRUPTURED OVARIAN PREGNANCY

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OVARIAN pregnancy is much more common than many assume. The total number of cases reported in the literature up to January, 1947, was eighty-eight.

In some of the cases that have been reported, a long period of sterility preceding ovarian pregnancy has been noted, as well as the presence of a co-existing endometriosis.

The patient is a married woman, aged 30 years, well nourished, normally developed, and of medium build. She had an appendectomy at the age of 13 years, after several attacks of what was diagnosed as recurrent appendicitis. She had the usual childhood diseases, without complications. Patient had been married for nine years, was never pregnant, and had never used contraceptives.

Menstrual history: onset at 11 years of age, duration 3 to 4 days. Her menstrual periods have been irregular in recurrence since onset, usually had an interval of 42 to 46 days between periods. At times, she experienced cramplike lower abdominal pain with headache before the flow was established, but never experienced severe pain, and has always been able to perform her usual duties without much discomfort throughout the period, and her blood loss was moderate in amount.

Her last normal menstrual period was from Sept. 3 to 7, 1947. She noticed a vaginal discharge on October 16, 1947, and passed a few small clots. She described the discharge as dark in color, and scant in amount for the first day of a period, but was of the opinion that this was the start of a normal period beginning as usual about 14 days late. She continued to have menstrual bleeding after the usual three days. About the fifth day, she developed pain, cramplike in character, in her lower abdomen. She stated that she had "contracted a cold" and attributed her lower abdominal pain to "sore abdominal muscles."

The patient came to my office Nov. 14, 1947. She stated that she had continued "menstruating since October 16, 1947, and was advised by friends to consult a physician about it."

Her temperature was 98.2° F., pulse 84. Blood examination red blood cells 3,600,000, hemoglobin 76 per cent, white blood cells 7,700 polymorphonuclear leucocytes segmented 69 per cent; polymorphonuclear leucocytes nonsegmented 10 per cent; lymphocytes 17 per cent; monocytes 2 per cent; eosinophiles 2 per cent. Blood serology was negative by both Wassermann and Kahn tests; Rh factor was positive. Blood type B or 3. Catheter specimen of urine revealed the presence of 1 to 2 white blood cells per high-power field and a few squamous epithelial cells. Albumin and sugar negative.

Examination of the abdomen disclosed moderate tenderness over the lower right abdomen. Vaginal examination revealed a scanty bloody discharge. Introitus was marital, nulliparous in type. Speculum examination of the cervix showed a mild erosion involving the endocervix and a Nabothian cyst on the anterior lip. The cervix was not particularly soft in consistency. The fundus was anterior. The uterus was slightly enlarged for a nullipara, but not unusually soft in consistency, and was freely movable, but displaced to the left by a soft cystic mass about 7 cm. in diameter, in the right adnexal region. The mass was tender to palpation and fixed in the cul-de-sac. A diagnosis of right ovarian cyst was made and operation was advised. While waiting for a hospital bed, the patient returned to her home about 20 miles from the city. On Nov. 18, 1947, she complained of severe abdominal pain, intermittent and cramplike in character, and passed material from the vagina and was having

rather free vaginal bleeding. A local physician was called to her home and notified me that he thought that she was having an abortion, since the material passed had the gross appearance of decidua.

Pathologist's report: decidua.

The patient was admitted to the hospital Nov. 20, 1947, and was re-examined. The tender right adnexal mass was no larger. The uterus was of the same size and consistency as at the previous examination, but because of the passage of decidual tissue, a diagnosis of ectopic pregnancy was made and operation advised. With the patient under sodium Pentothal and spinal anesthesia, a low midline incision was made and the abdomen opened. The omentum was found attached to the right adnexal mass but was readily freed. The mass occupied the position of the right ovary, was about 8 cm. in diameter, and was adherent to the posterior surface of the broad ligament at the base in the cul-de-sac. The right tube was found stretched over the tumor mass. The left ovary was normal. The left tube showed evidence of an old perisalpingitis, and the fimbriated end appeared to be closed. The uterus was normal in size and normal in consistency but pushed to the left by the right adnexal mass. The mass was freed by finger dissection and removed by clamping, cutting, and ligating the infundibulopelvic ligament, mesosalpinx, and Fallopian tube.

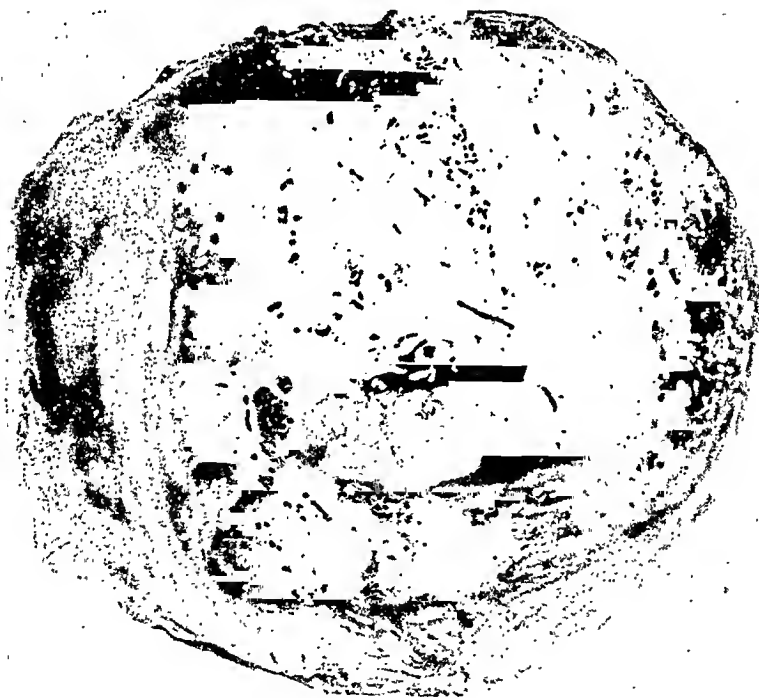


Fig. 1.—Ovarian mass opened, showing an embryo 2.5 cm. in length.

The tumor, after removal, had the gross appearance of an endometrioma of the ovary. Careful inspection of the cul-de-sac, uterosacral ligaments, and the peritoneum covering the rectum and sigmoid did not disclose any evidence of ectopic endometrial implants. The left ovary was normal. The specimen was incised and a spherical cavity was found in the center of the tumor. The sac lining the cavity was incised and found to contain an embryo. The sac was filled with clear liquid, lined by a smooth, glistening membrane. The embryo was curled and supported by filmy membranes and a clearly distinguishable body stalk attached near the caudal end. A postoperative diagnosis of unruptured ovarian pregnancy was made.

Pathologist's Report—Gross.—Specimen of ovary measuring 8 by 8 by 6 cm. A Fallopian tube is attached to the ovarian mass. The tube is dissected throughout its course and found to open freely to its fimbriated end, which is adherent to the surface of the ovarian

mass. There is no abnormality of the mucosa which would suggest a decidual reaction. Section of the ovarian mass reveals a cavity 6 cm. in diameter, which contains an embryo 2.5 cm. in length. The wall of the cavity is hemorrhagic and measures 2.5 to 1 cm. in thickness. The mucosa shows no abnormality.

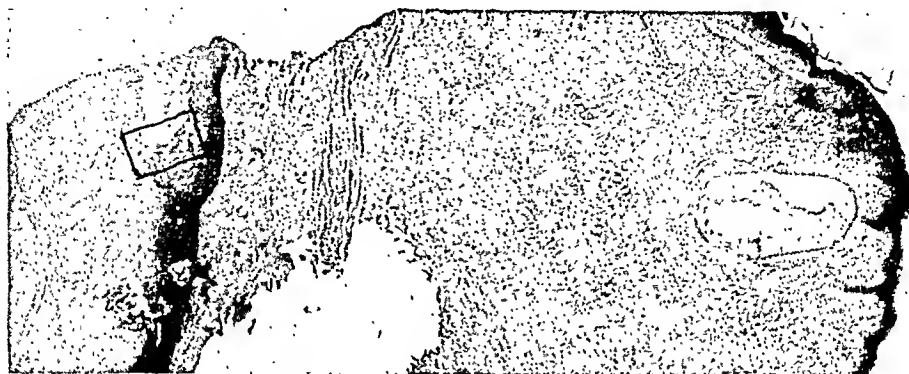


Fig. 2.—Photomicrograph of tissue surrounding the sac, showing follicle cyst at right (X12).



Fig. 3.—Magnification of area outlined in Fig. 2, showing chorionic villus (X130).

Microscopic.—Section from ovarian mass reveals ovarian tissue with decidua and chorionic villi and hemorrhage. In the section of the tube adherent to the ovary, there is a small focal area of decidua but no chorionic villi. This decidua is similar to the decidua found in the specimen passed per vaginam. Inasmuch as decidual change occurs in other organs in ectopic pregnancy, it may be concluded that this represents such a change. Although the finding does not completely exclude the possibility that this ovarian pregnancy had its origin at an earlier period in the Fallopian tube, this latter conclusion is rather remote.

Diagnosis.—Compatible with primary ectopic ovarian pregnancy.

Comment

The passage of a decidual cast per vaginam, which microscopically showed the presence of decidua with an absence of chorionic villi might have established the diagnosis of ectopic pregnancy. However, the old theory that, in the presence of ectopic pregnancy, the endometrium always undergoes decidual transformation cannot be maintained. The absence of decidual tissue in the uterus cannot be used as a diagnostic criterion, while, conversely the presence of decidual tissue without intrauterine pregnancy is practically always indicative of ectopic gestation, since its only alternative cause is the very rare corpus luteum cyst.¹ The

consistency of the cervix and uterus on examination and lack of early symptoms of pregnancy were misleading. The formation of decidua in the normal tube during pregnancy is unusual, but according to Kermauner, decidua is found in about 15 per cent of tubes. That a limited decidual reaction may occur, however, has been shown by Williams,² who found decidual cells in the opposite tube, where they could not be confused with cells of fetal origin.

The macroscopic and microscopic examination of the specimen proves it to be an unruptured ovarian pregnancy, and is compatible with primary ectopic ovarian pregnancy. The small focal area of decidua found in the section of the tube adherent to the ovary did not contain chorionic villi, and resembled the decidua found in the specimen passed through the vagina which did not show chorionic villi. There is a possibility that this ovarian pregnancy may have had its origin at this site in the Fallopian tube, but this seems rather remote.

The pathologist was unable to find any evidence of endometriosis in the sections studied. It is interesting that this patient gave a history of a long period of sterility prior to the ovarian pregnancy and that the microscopic examination of the specimen showed follicle cysts, varying in size, in the portion of the mass with intact stroma—a finding which has been noted in other reported cases.

Dr. John W. Howard, Pathologist, Delaware Hospital, Wilmington, Del. made the pathologic examinations.

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BILATERAL OVARIAN FIBROMA

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ACCORDING to recent reports fibromas constitute from 1.5 to 5 per cent of ovarian neoplasms.¹⁻³ In the series studied by Dockerty and Masson, about 10 per cent of ovarian fibromas were bilateral.¹ The relation of ovarian tumors and of fibromas in particular to the presence of fluid in the peritoneal and pleural cavities, the so-called Meig's syndrome, is the subject of numerous communications.^{4,5} In this paper the clinical history is presented of a woman past 70 years of age who had large bilateral ovarian fibromas; their presence was not associated with ascites and hydrothorax.

C. M. E., a white woman, aged 73 years, was admitted to the University of Oklahoma Hospitals, Sept. 25, 1945, with complaints of pain and masses in the abdomen and loss of weight and strength. She stated that about three years prior to admission she first noticed a mass about the size of a golf ball in the right lower abdomen. About two months later another similar mass appeared on the left side. These masses enlarged progressively and apparently increased in size more rapidly during the past one and one-half years. During the past few weeks pain appeared radiating into the right lower limb, and became severe, limiting her activities. She had lost some weight and strength.

Menarche occurred at the age of 16 years, the interval was regular, lasting twenty-six days, with the flow four to five days. She had seven pregnancies with no abortions, and reached the menopause at the age of 45 years. She had always been in good health and had no previous operations.

At the time of admission she was well developed, well nourished, and appeared about ten years younger than her stated age. She was not acutely ill. The temperature was 99.4° F.; the pulse rate was 88; the respiratory rate 20; the blood pressure was 150/100. The abdomen was medium sized and flat. In the lower abdomen three masses were visible and palpable, one on the left was about 12 by 9 cm., another just above the symphysis pubis was smaller and not freely movable, the third, which was 17 by 12 cm., was on the right and extended up toward the flank. This mass was freely movable and the site of its attachment could not be determined. There was moderate tenderness on palpation. Pelvic examination revealed a parous introitus with the cervix scarred bilaterally. There was no discharge. Movement of the left and suprapubic masses was transmitted to the cervix. There seemed to be no connection between the right mass and the pelvic organs.

The urine was yellow, turbid, acid, with a specific gravity of 1.017, and with no albumin and no glucose. There were 20 white blood cells per h.p.f. The red blood cell count was 4,140,000, the hemoglobin content 13 Gm., the white blood cell count was 8,400 with granulocytes 74, and lymphocytes 26 per cent. The Mazzini test of the blood was negative. Retrograde pyelograms on October 2 revealed both kidneys to be of normal size, shape, and position, with no changes in the calices and renal pelves. Smears of the urinary sediment of the right kidney contained no organisms; a few gram-negative bacilli were seen and cultured from the urine of the left kidney. Electrocardiogram examination on October 4 disclosed primary T-wave changes of a nonspecific kind, not considered a contraindication for operative procedure. Roentgenologic examination revealed no fluid in either pleural or pericardial cavity; calcification of the aortic and mitral valves and of the

abdominal blood vessels was seen. Examination of the gastrointestinal tract disclosed complete emptying of the stomach in five hours, diverticula of the colon and no connection of the pelvic masses with the digestive tract.

Laparotomy on October 5 (by Dr. Oscar R. White) disclosed replacement of each of the ovaries by similar, firm, globular masses. That on the right was about 5, that on the left 4 inches in diameter. The uterus was of usual size and appearance. The Fallopian tubes were stretched over the respective ovarian masses. There was no excess fluid in the peritoneal cavity. A bilateral salpingo-oophorectomy and appendectomy were performed. The postoperative course was uneventful and the patient was discharged October 23, the eighteenth day following the operation. When last seen March 23, 1946, five months after the operation, she was well and had no pertinent complaints.

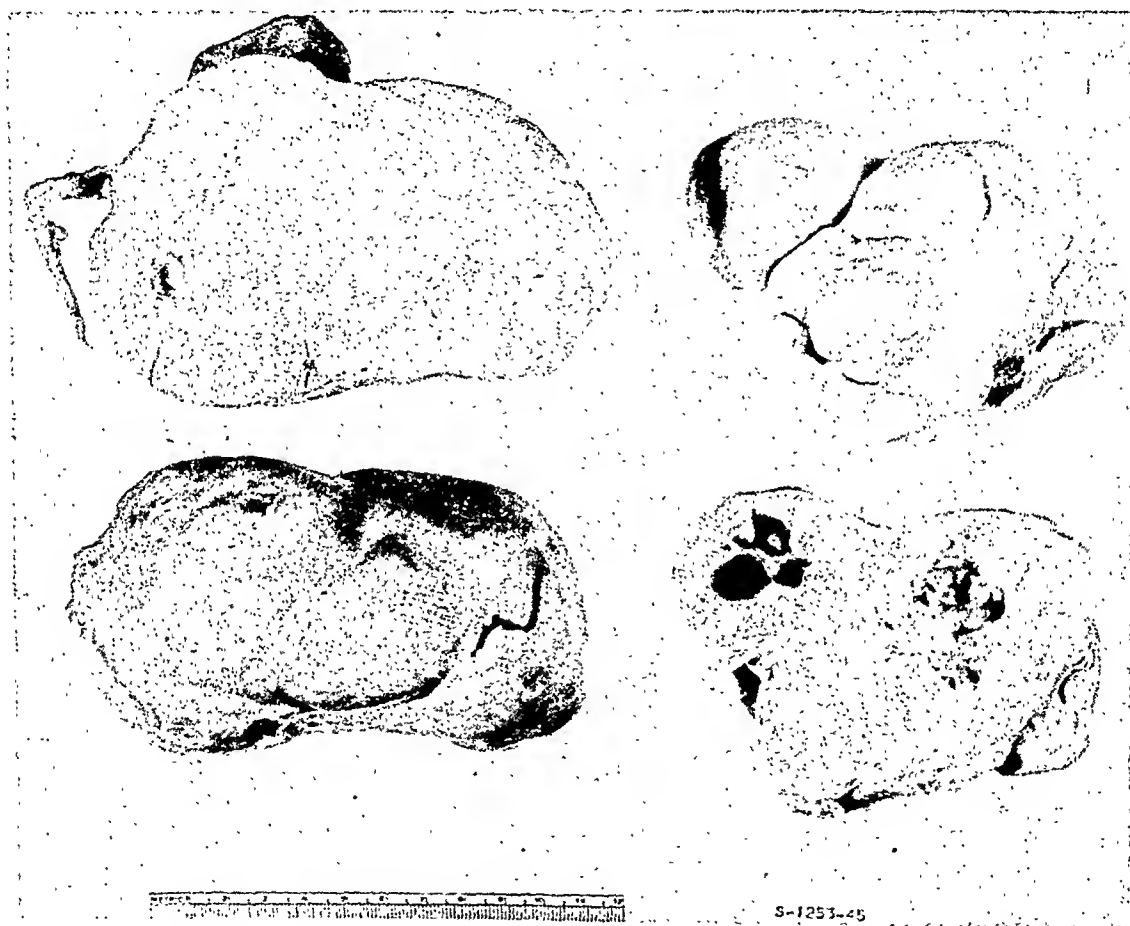


Fig. 1.—Gross appearance of the ovaries externally and on their cut surfaces. The larger one is the right ovary.

The specimen consisted of both Fallopian tubes and ovarian masses and the appendix. In place of the right ovary there was a solid lobulated mass measuring 12.5 by 10 by 8 cm. and weighing 610 grams (Fig. 1). The surface was smooth and shiny. The cut surfaces were uniform gray white with a delicate fibrillar pattern. No areas of softening or discoloration were evident. The Fallopian tube measured 12 by 1 by 0.4 cm.; its fimbriated end was patent, it appeared somewhat stretched and laterally compressed. The mesosalpinx was delicate. The left ovary was replaced by a solid mass, 10.5 by 9.5 by 7 cm. weighing 324 grams. It resembled the right except that the surface of the ovarian mass was more lobulated; the lobules measured 3 to 5 cm. in diameter. The cut surfaces had a similar or more coarse fibrillar pattern with occasional cavities from 0.5 to 2 cm. in diameter

containing a thick, clear, or hemorrhagic liquid (Fig. 1). The left Fallopian tube with mesosalpinx resembled the right. The appendix was 3 by 0.5 cm. and part of its lumen was obliterated.

Microscopic preparations from various parts of each of the ovarian masses disclosed round or elongated cell nuclei within a delicate fibrillar ground substance in an interlacing arrangement closely resembling ovarian stroma (Fig. 2). Elsewhere the texture was loose; the fibrils were spread apart with occasional collagenous bundles and with cells having vesicular nuclei and a stellate cytoplasm fading into the fibrillar ground substance (Fig. 3). Hyaline change was more marked in some fields than in others. There were also extensive areas of lavender stained granular deposits in the larger hyalinized fields. Apparent remains of corpora albicantia appeared here and there. Over extensive areas a cellular debris was encountered fading into the adjacent tissue with hardly any cellular reaction.

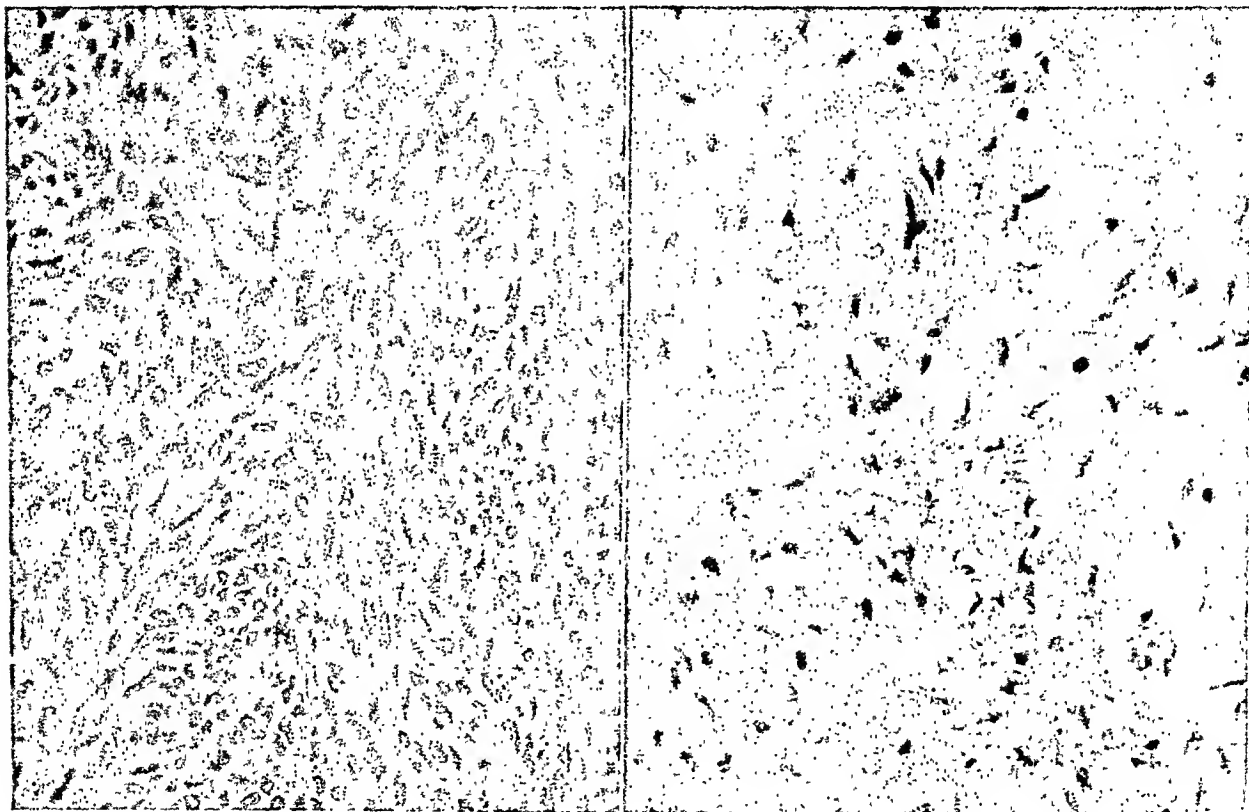


Fig. 2.

Fig. 3.

Fig. 2.—Microscopic appearance of the ovarian neoplasm. Round or elongated cell nuclei are seen in a steam or whorl-like arrangement within delicate fibrils. ($\times 300$.)

Fig. 3.—Microscopic appearance of the ovarian neoplasm. Cells with vesicular nuclei and a stellate cytoplasm are seen fading into a fibrillar ground substance. ($\times 300$.)

Comment

Ovarian neoplasms occur in all decades of life, but are more frequent during the reproductive period.³ The stimulation for the cyclic changes in the ovaries is known to be extrinsic. The parent cells of most neoplasms occurring in the ovaries arise from the germinal epithelium or its derivatives. Therefore it is safe to assume that hormonal stimulation is responsible for the reaction of the germinal epithelium. Ovarian neoplasms are comparatively rare in children before the onset of menstruation and in women after the cessation of menstruation. The hormonal influence regulating ovarian function is least potent during postmenopausal life. Neoplasms arising in the ovary at this period of life are therefore usually of stromal origin.

Our patient was past the seventh decade of life. The large growths in the ovaries were almost alike with identical microscopic structures and with complete absence of epithelial elements.

Summary

Fibroma of both ovaries is reported in a 73-year-old white woman. The large growths appeared grossly almost alike and microscopically they mimicked ovarian stroma. They contained no epithelial elements. There was no associated ascites and hydrothorax.

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ENDOMETRIOSIS OF THE VAGINA FOLLOWING VAGINAL HYSTERECTOMY

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THIS is a case report of endometriosis of the vagina following vaginal hysterectomy. Because of its rarity, we felt it worth while reporting.

In a review of 800 cases of vaginal hysterectomies at the Cook County Hospital, we failed to find a similar complication; also Green-Armytage 627 cases; N. Sproat Heaney 627 cases; 517 cases by Danforth; 305 cases by Tyrone and Weed; 210 cases by Cofer; and 500 cases by Falk and Bunkin failed to reveal a similar complication. However, we did find one case report in the *Polish Medical Gazette*.¹

Case Report

A 39-year-old Negro woman, of good general health, was admitted to the Gynecological service of Cook County Hospital in March, 1945, with a complaint of excessive vaginal bleeding for seven days past. History revealed a change in the menstrual habits of the patient in the preceding three months, her flow becoming excessive in amounts and persisting for a longer period, up to eight days. Past menstrual history indicated that at the age of 14 years the menarche began, it being characterized by a regular cycle of five days, moderate flow, with no dysmenorrhea either primary or acquired. Obstetric history revealed a gravida iv, para iii, including a normal spontaneous delivery in 1923, a breech delivery in 1924, and a normal spontaneous delivery in 1926. There was a three months spontaneous abortion in 1925. Pelvic examination elicited a small, nodular corpus, freely moveable, not tender, adnexal findings not revealing, and a relaxed posterior vaginal wall. Other physical findings were noncontributory, or otherwise negative. Blood pressure was 120/80, pulse was 84, respirations were 20, and temperature was 98.6° F. Hemoglobin was 75 per cent, 4,300,000 erythrocytes, 8,100 leucocytes, urine negative, and negative serology.

A vaginal hysterectomy without morcellation and a posterior colporrhaphy were performed. The postoperative course was uneventful. The patient left the hospital in good condition, symptom free. Final postoperative six-week examination was essentially negative.

Three months following the vaginal operation the patient noted what seemed to her to be a return but definite diminution of her menstrual periods. There was a show of blood which was cyclic in its appearance, in keeping with her previous menses. After two years and seven months of these cyclic episodes following her vaginal hysterectomy, the patient presented herself for examination to the outpatient Gynecological Clinic of Cook County Hospital in October, 1947.

Pelvic examination revealed a free pelvis: no masses, no fixations, no tenderness. Speculum examination revealed a flat, bluish area, about 4 by 6 mm., on the left posterior vaginal wall, immediately below the transverse hysterectomy scar (Fig. 1). The remainder of the vaginal vault was without findings. Suspicions were immediately aroused of the possibility of an endometriosis of the vagina. A biopsy of this suspected area was taken for histologic study. The biopsy report showed an endometriosis of the vagina (Fig. 2).

Forthwith, the pathologic report of the corpus and cervix removed at surgery in 1945 was reviewed. No evidence of endometriosis or adenomyosis was present at that time. Cystoscopic and proctoscopic examinations done in October, 1947, have not given indication of other ectopic endometrial implants.

It is quite probable that the endometrium was implanted during surgery.



Fig. 1.—High power view of group of cells extending into underlying stroma. Delineation is well established and little variation in staining properties apparent. ($\times 215$.)

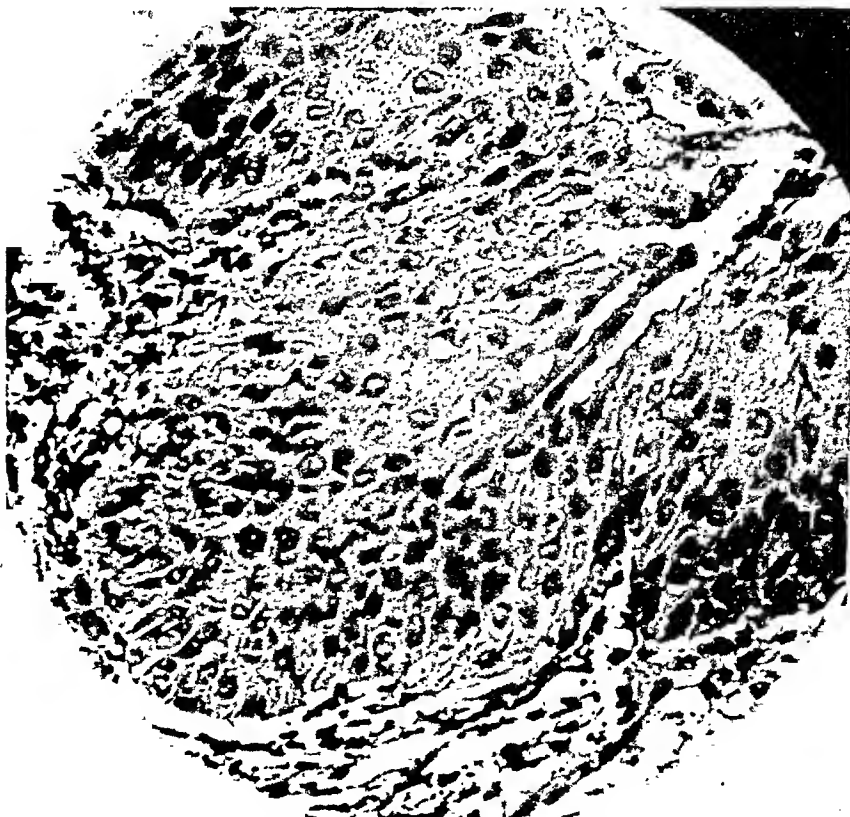


Fig. 2.—Portion of lining of endocervix removed at scalpel conization. This benign lesion shows uniformity of size and staining properties of the metaplastic cells. ($\times 215$.)

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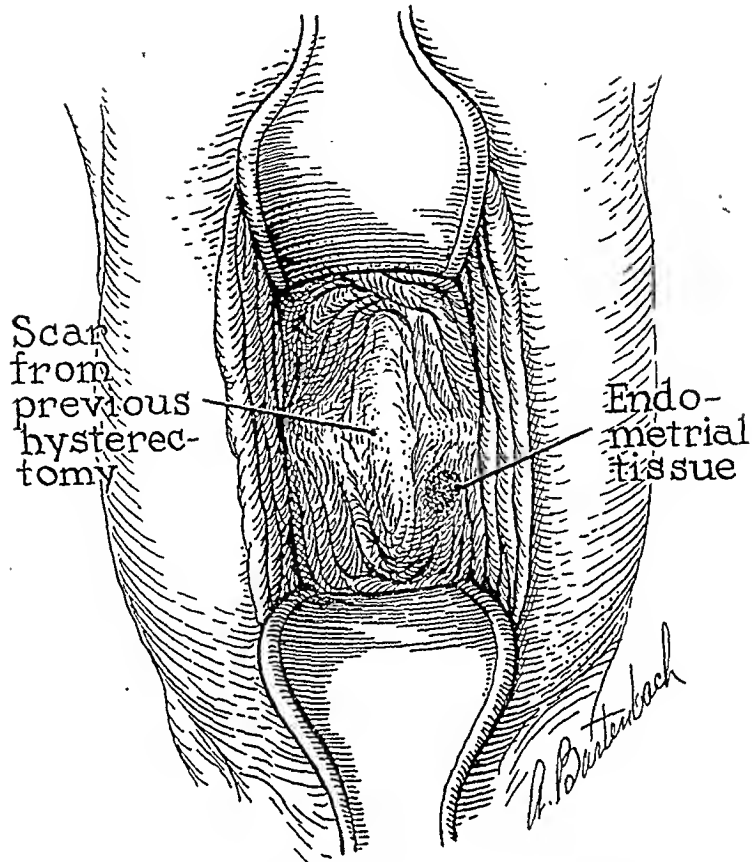


Fig. 1.—Artist's drawing showing the site of endometriosis.



Fig. 2.—Photomicrograph of biopsy showing endometrial tissue (×90).

ovary. But further exploration showed that both ovaries were intact, only that they were cystic. Since most of the bleeding came from the fundus of the uterus, we quickly did a subtotal hysterectomy and double salpingo-oophorectomy. After evacuating as much of the growth as possible and putting a firm gauze packing against the oozing surfaces, the abdominal incision was closed in the usual manner. Unfortunately, we could not give blood transfusion for lack of a donor or blood bank. We gave four units of plasma, before, during, and after the operation, and continuous venoclysis of glucose solution. The patient became conscious after the operation, but succumbed two hours afterwards.

Examination of the hysterectomized uterus showed a raw eaten-up fundus from which issued friable strands looking as if they had been pulled upwards. Sagittal section of the uterus showed that the endometrium was clean without any trace of the growth. Both ovaries had been converted into corpus luteum cysts the size of a goose egg.

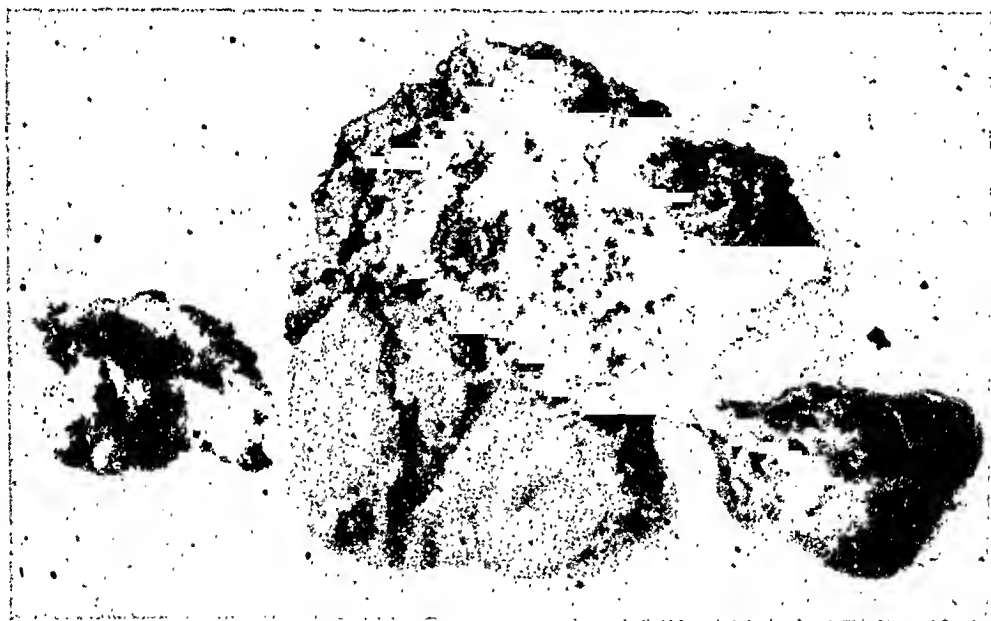


Fig. 1.—Chorionepithelioma. Uterus.

Autopsy revealed two more handfuls of growth attached to the intestines, omentum, and posterior parietal peritoneum. The lower lobe of the right lung showed a small focus of metastasis of the growth. Biopsy of the growth found in the lungs and abdominal cavity showed syncytium and Langhans cells with a predominance of the latter in some portions and of the former in other parts.

Comment.—Apparently, the condition began as a myometrial chorionepithelioma which later extended to the right broad ligament and which rapidly grew in size. It was only in the last days, when the chorionic cells had extended themselves beyond the confines of the broad ligament and serous surface of the uterus that internal bleeding, tympanism, abdominal pain supervened rapidly, threatening the life of the patient.

Our inability to make preoperatively the correct diagnosis was due to the following: (1) Because when first seen, the size, consistency, and contour of the growth was suggestive more of uterine fibroid than of anything else. (2) The failure to associate the growth with the four months' abortion which took place seven months before she complained of bleeding. (3) The misinterpretation of the uterine bleeding that occurred later as part of the phenomenon of uterine fibroma. (4) The fact that she was in relatively good condition on admission, in spite of the advanced condition of the growth. Because we erroneously thought chorionepithelioma was a remote possibility, no Friedman test was made. The reason the patient here reported did not have early peritoneal bleeding, in spite of its being a myometrial growth that had gone beyond the uterus, is because the chorionic cells grew within the leaves

UNSUSPECTED ABDOMINAL CHORIONEPITHELIOMA

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EVER since we lost practically all cases of chorionepithelioma, which were diagnosed only at autopsy, we had been vigilant of their occurrence and, in recent years, have felt the satisfaction of having saved many lives because of early diagnosis, making possible early radical treatment. So our failure to make the correct diagnosis in the present case, though markedly advanced when first seen, showed that we have much yet to learn about chorionepithelioma.

L. P., 27 years old, laundress, entered the Philippine General Hospital on Sept. 13, 1947, because of an abdominal painless tumor. The patient claimed that she first noticed the tumor as an apple-sized mass in the lower abdomen, five months previous to admission. And at the same time, she also noticed that she began to have slight vaginal bleeding which was continuous for two and one-half months but which stopped for two months thereafter. However, the last two weeks before admission, the slight bleeding reappeared off and on. During this time, she also experienced slight afternoon rise of temperature.

She had had three pregnancies, the first two of which ended in full-term deliveries ten years and five years, respectively, before admission. The third pregnancy ended in a four months' abortion one year previous to admission. Menstrual periods after the abortion were normal, the last one occurring one month before the onset of the slight continuous bleeding.

Physical examination showed that she was fairly well nourished though rather thin. Lungs and heart were apparently normal. The abdomen showed a large, firm, painless, slightly movable, globular tumor reaching up to the level of the umbilicus, the size of a six months' pregnancy. On vaginal examination, one could feel a small cervix connected with the uterus which was flattened and pushed to the left and posterior fornices by the large firm mass. There was slight pinkish discharge from the external os.

Red blood count, 3,900,000; white blood count, 9,650; polymorphonuclear leucocytes, 77 per cent; lymphocytes 23 per cent. Urinalysis normal. Blood pressure 110/70.

Because of the finding of a firm, solid painless mass in the abdomen which was independent but intimately connected with the uterus, our first impression was a large subperitoneal fibroid. We could not, however, reconcile the diagnosis of a subperitoneal fibroid and the rapid growth of the tumor, which was noticed only five months previous to admission. But we felt that perhaps the tumor had existed unnoticed for sometime. Because of the rapidity of the growth, we considered the possibility of a malignant tumor of the ovary. Chorionepithelioma was considered, but was immediately dismissed because of the firm consistency of the tumor and because the uterus could be distinctly outlined as separate from it. The patient was, therefore, scheduled for operation three days later. On that day, however, she had cough and fever. In the belief that she was suffering from influenza, she was treated for this condition and the operation was postponed. But the fever, which was irregular, did not abate. On the contrary, as the days advanced, it became higher. Moreover, the patient began to complain of abdominal pain, tympanism, nausea and vomiting. At this time, we thought that what we regarded as a tumor was perhaps an encapsulated abscess which now began to leak into the peritoneal cavity and which needed immediate laparotomy, which was done on Oct. 2, 1947, under local anesthesia.

On making a small incision on the peritoneum, an encapsulated mass looking like a large endometrial cyst was found. Aspiration revealed bloody content. After enlarging the abdominal incision and trying to evacuate the contents, we encountered a bloody mass of many small, firm, loose pieces of tissue attached to the intestines, omentum, uterus and posterior parietal peritoneum. We then thought we were dealing with a malignant growth of the

BILATERAL SIMULTANEOUS EXTRAUTERINE PREGNANCY*

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EXTRAUTERINE pregnancies are estimated by Schumann¹ to occur once in every 300 pregnancies. Bilateral simultaneous extrauterine pregnancies occur many times less often. They are considered the rarest form of double-ovum twin pregnancies. Therefore, the occurrence of an authentic case which meets the criteria for acceptance, as stated by Fishback,² is rare enough to merit its being reported.

In 1935, Fitzgerald and Brewer³ reported on 402 cases of extrauterine pregnancies from 1924 through 1934; in 1942, Lash and Kaufman⁴ reported on 903 cases through 1940, and Fitzgerald⁵ has collected an additional 274 cases from 1940 through 1946, all from this hospital, and in these groups no bilateral double ovum ectopic pregnancy was found. Lash and Kaufman reported on the only instance of an unilateral twin ectopic pregnancy to have occurred at this institution. One of us (R.A.A.) has reviewed the cases of extrauterine pregnancies for the years not included in the above reports for an additional 403 cases. The case herewith, therefore, is the first bilateral simultaneous extrauterine pregnancy to be proved at this hospital in a total of 1,580 extrauterine pregnancies over a twenty-two year period.

Mrs. L. Mc, a 32-year-old, well-developed, well-nourished Negro woman who was not acutely ill, was admitted to the gynecologic service on Oct. 24, 1947, complaining of irregular vaginal spotting for the past two months and a dull lower abdominal pain for the same period. Her last normal menstrual period had occurred in August, 1947. Her September period started at its expected date, continued for two days, stopped for two days, following which the spotting started again and continued for another seven days. Shortly after the onset of this irregular period, the patient noted a dull lower abdominal pain which radiated into both right and left lumbar regions. The next period (October) began several days before its expected date and continued irregularly throughout the month. The abdominal pain remained unchanged.

The patient was a gravida iv, para iii, a spontaneous abortion having occurred in 1940. The menarche began at 13 years, of regular interval, lasting for four days, with no dysmenorrhea.

On admission, the temperature was 98.6° F., pulse 80, respirations 20, blood pressure 110/80. The erythrocyte count was 4,100,000, the leucocyte count 9,550, and the serologic reaction was negative. Abdominal examination revealed moderate tenderness in the right lower quadrant, no masses being outlined. Bimanual examination revealed a tender, cystic, right adnexal mass. The left adnexa felt thickened and was also tender. The corpus was enlarged two to three times its normal size and was firm and nodular. A diagnosis of fibroid uterus with pelvic inflammatory disease was made.

At laparotomy, the corpus was found to be in good position, about twice normal size and nodular. The right tube was drawn backward toward the right infundibulopelvic ligament and had a hemorrhagic mass, measuring 4 by 3 by 3 cm., in its isthmic portion. Its fimbriated end was free and not involved. The left tube was directed downward and backward toward the cul-de-sac, its fimbriated end having been replaced by another hemorrhagic, cystic mass, measuring 6.5 by 3 by 3 cm., which was rather firmly attached to the rectum.

*Presented before the Chicago Gynecological Society, Jan. 16, 1948.

of the broad ligament which at first constituted itself as a firm capsule, giving shape and firm consistency to the growth in the same manner as happens in intraligamentous ovarian conditions or even pregnancy.

The long interval of seven months that elapsed between her abortion and the occurrence of the abnormal vaginal bleeding is not unusual. From our experience with myometrial chorionepithelioma, in 55 per cent of the eight cases we had in 1942 to 1945, the vaginal bleeding did not manifest itself until from one year and two months to three years after the passage of the last product of conception which happened to be hydatidiform mole. Two of these cases were preoperatively diagnosed as cancer of the uterine corpus and two, because of symptoms of internal bleeding on admission, as ruptured tubal pregnancy.

Had we seen the patient when she began to have continuous bleeding, had we felt the small mass in the lower abdomen, and associated such findings with her last abortion, we would have been able to diagnose her condition by the clinical method of diagnosis of uterine chorionepithelioma as first described by me.² Even if our diagnosis then had been fibroma, she would have been saved by immediate laparotomy, which would have revealed the true condition of the uterus.

If the correct diagnosis of abdominal chorionepithelioma had been made on her admission, what treatment should have been instituted? I believe the only hope for the patient then was x-ray treatment both for the abdominal and pulmonary growths.

The author is greatly indebted to Dr. Apelo, who furnished the photograph of the uterus.

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Discussion

The review of authentic cases presented by Fishback in 1939 brought the literature up to date and set the standards of acceptance for these cases. Fishback collected 76 cases and reported on one of his own, a twin ectopic pregnancy on the left and a single one in the right tube at the same time. His principles for acceptance require that "there should be a description of the fetuses or any portion of them found, as well as of placental material. A microscopic examination may be necessary to confirm the diagnosis and to give criteria for fixing the pregnancy periods. Especially is this needed where only a hematosalpinx is present grossly."

Harris and Leviton,⁶ in 1946, surveyed the literature since 1939 and presented an additional eight authentic cases of bilateral simultaneous tubal pregnancy, making a total of 85, including one of their own.

As far as was possible, the accessible literature was reviewed by us and other authentic cases not included in the above reports were found. They include single cases by Olovson⁷ (1938), Pasman and Lovazzano⁸ (1938), Froewis⁹ (1939), P. Meyer¹⁰ (1939), Trautenberg¹¹ (1944), Weyeneth¹² (1945), MacDonald and Masters¹³ (1946) and Gorman¹⁴ (1947). These cases, plus the one here reported, make a total of 94 authentic cases of bilateral simultaneous tubal pregnancy. Other cases no doubt are included in other foreign literature, but their distribution has been delayed by the recent war.

The preoperative diagnosis of bilateral simultaneous tubal pregnancy is a difficult one to make. Froewis is the only one noted to have made the speculative diagnosis of a "probable bilateral tubal pregnancy." Since the bilaterality of an ectopic pregnancy is so rarely diagnosed before surgery, the practical significance to be stressed is that both adnexa should be inspected and palpated at the time of operation.

We are indebted to Dr. Alex B. Ragins of the Department of Pathology, Cook County Hospital, for his assistance with the microscopic report.

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There was no free blood in the peritoneal cavity. With the pathology at hand and the patient's condition being good, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed.

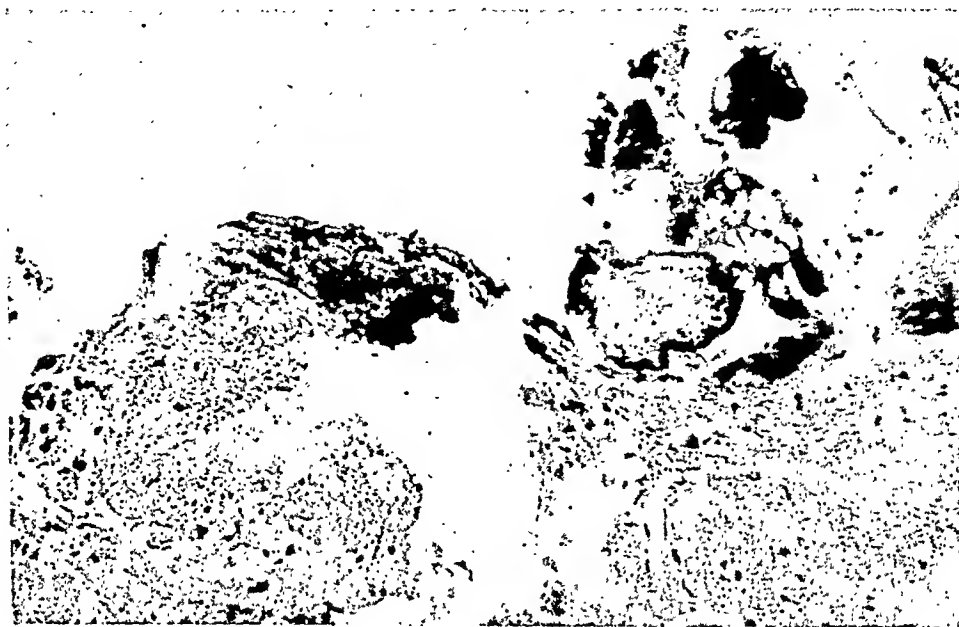


Fig. 1.—Right tube section.



Fig. 2.—Left tube section.

The postoperative course was uneventful and the patient left the hospital in good condition. Microscopic study of the cystic masses in each of the fallopian tubes revealed the presence of chorionic villi, approximately at the same developmental stage, indicating a simultaneous bilateral tubal pregnancy to have been present. (Figs. 1 and 2.)

Under general anesthesia the abdomen was opened. About 1,500 cubic centimeters of blood was aspirated from the abdomen. The sigmoid was found to be tightly adherent to the superior posterior portion of the uterus, which was bulging into a conical shaped mass predominately left sided. The sigmoid was partially separated from the uterus, and there was gross hemorrhage into the uterine wall with rupture of the uterus at this point. An incision was made enlarging the point of rupture and a well-formed fetus of about four months' gestation was removed. The sigmoid was then separated from the uterus, and a Porro section accomplished without further difficulty. During the operative procedure typed and matched blood was given continuously. The patient was in shock during the entire operative procedure, and left the operating room in poor condition. She was given a second infusion of compatible blood immediately after operation and her condition improved rapidly, blood pressure rising to 98/40. From this point on, the convalescence was uneventful, and the patient was discharged from the hospital on the thirteenth postoperative day.

The pathologic report showed a uterus amputated at the internal os having an odd lop-sided shape. The left border bulged into a conical shape, having for its apex the ovary. The fixed specimen measured 14 cm. by 10 cm. by 6 cm. The cavity in the fundus extended into the conical shaped bulge, but ended abruptly, being supported by a firm layer of uterine wall 1 cm. thick. Serial sections revealed a rough cavity partly collapsed within the uterine wall, but not contiguous with the uterine cavity. Part of this cavity was surrounded by uterine muscle. The top was supported by broad ligament, and the apical border was formed by the left ovary which in turn was incorporated by the walls of the uterus. The cavity was rough, being lined by fragments of placenta and clotted blood, and contained a well-formed placenta with cord. The stump of the right broad ligament was close to the uterus. The microscopic examination showed a decidual reaction of the endometrium and a decidual stroma in the wall containing well-formed chorionic villae.

Diagnosis.—Extrauterine pregnancy, probably in the cornu of the uterine wall (interstitial), expanding laterally with rupture into the fold of the broad ligament and peritoneal cavity.

INTERSTITIAL PREGNANCY

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AMONG the varied types of ectopic pregnancy encountered, one of the least common, but yet more serious varieties, is the interstitial pregnancy. This type is probably exceeded in rarity only by the true ovarian pregnancy, and it makes up not more than 3 per cent of all ectopic pregnancies.

An interesting case of interstitial pregnancy, with an unusual feature, is herewith reported.

Mrs. L. M. (No. 75279), 30-year-old white female, was admitted to the hospital on Sept. 2, 1946, complaining of severe knifelike pain in the lower abdomen with radiation to the left shoulder. The onset was 9 A.M. of the admission date.

The present illness dated back to the June 9, at which time the patient had a dark brown thin vaginal discharge for one week. There was no pain or cramps associated with the discharge. Her last regular menstrual period had been on May 3. In July she had severe lower abdominal pain lasting several hours, which gradually subsided completely. Following this episode she consulted her obstetrician who suspected a pathologic pregnancy, since examination revealed the uterus to be irregularly enlarged in the left cornual region.

A consultant confirmed the findings already mentioned, and advised that the patient be carefully observed and conservatively treated at present. Accordingly, the patient was given progesterone and was watched.

On the morning of hospital admission the patient suffered severe knifelike pain in the lower abdomen referred mildly to the left shoulder. When admitted to the hospital two hours later she did not appear acutely ill. Temperature, pulse, and respirations were normal, and the blood pressure was 110/65.

The menstrual history revealed a normal thirty-day cycle. Her last regular menstrual period was May 3 lasting four days, and her previous period was on April 6 lasting four days. The patient had been married for seven years, her first pregnancy in September, 1942, terminated as a ruptured left tubal pregnancy. This tube was removed at operation. There were no subsequent pregnancies until the present one.

Examination of the abdomen revealed a mass, undoubtedly the uterus, which seemed to be drawn into the left lower quadrant, the height of the fundus being 15 cm. above the symphysis. The left cornual area was enlarged, tender, and firm. Rectal examination revealed a thick undilated cervix. Urinalysis was essentially negative and the red blood count was 3.03 million with 8.1 Gm. of hemoglobin. The Rh factor was negative.

In view of the rapidly improving general condition of the patient, and the strong desire of the patient to have a child, watchful waiting seemed advisable. The mass in the abdomen was checked frequently, and blood pressure, pulse, and respirations were recorded at frequent intervals.

The temperature ranged between normal and 99° F. The pulse between 64 and 80 and the blood pressure between 92/60 and 110/60. The patient was kept at bed rest with an ice cap to the abdomen, codeine and aspirin given in small doses, and progesterone in adequate dosage.

Under this regime the patient rapidly improved. A transfusion of one pint of compatible blood was given, and the pain rapidly subsided to a low-grade dull ache in the left lower quadrant. The patient was permitted to sit out of bed on the third hospital day. She was completely free of pain at this time, and the mass in the lower abdomen lost its tenderness and became much softer.

On the sixth day of her admission about 9:00 P.M., and following an effective bowel movement, the patient complained of severe lower abdominal pain. The abdomen was rigid and exquisitely tender. Blood pressure dropped to 60/34, the pulse was 80, but volume was poor. The skin was cold and moist. The patient was prepared for immediate operation.



Fig. 3A.—Rebiopsy three days later showing blending of normal endocervical lining with full thickness of atypical cells. ($\times 50$.)

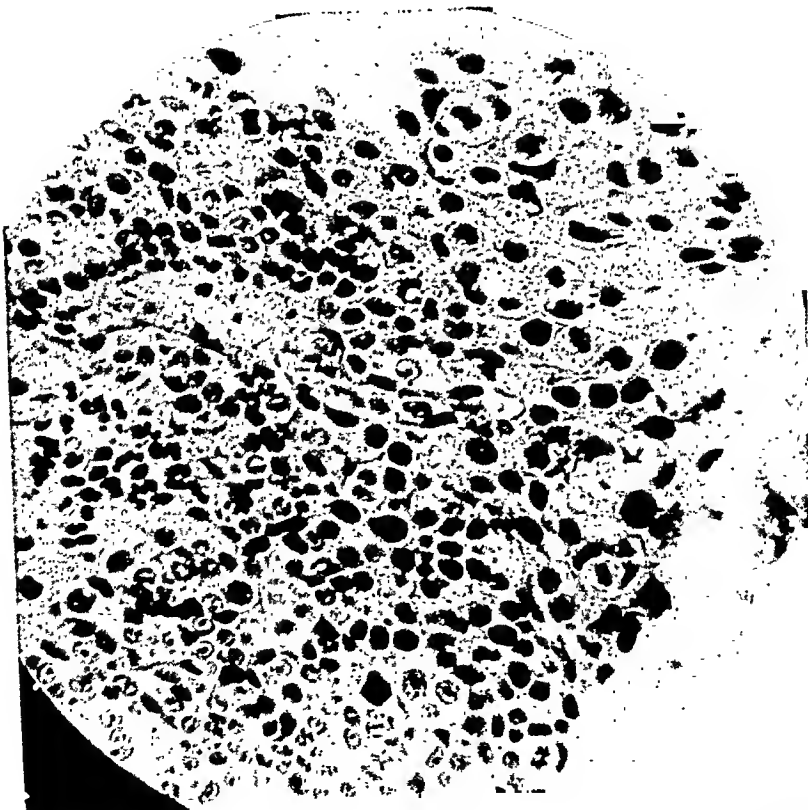


Fig. 3B.—Marked variations in size, shape, and staining property of cells. Mitoses are common. ($\times 215$.)

Department of Reviews and Abstracts

Selected Abstracts

Cancer, Malignancies

Cusmano, L.: Nuclear Aspects in Crushed Cancer Tissue With Carmine Stain, *Atti della Societa italiana di ostetricia e ginecologia* 37: 167, 1946.

Structure and chemical make-up of chromosomes and nucleoli differ in cancer and in physiologic tissue. Selective absorption for ultraviolet light and selective staining properties of timonucleinic acid, the main component of the chromosomes, versus ribonucleinic acid, the main component of the nucleoli, made it possible to demonstrate this.

Investigations of cancer tissue made in ultraviolet light by Caspersson and Santesson resulted in the recognition of two main types of cells: "A" cells, as compared with healthy cells, show an increased content of timonucleinic acid and therefore have condensed and prominent chromosomes. "B" cells, that show diminution of timonucleinic acid and, therefore, have indistinct chromosomes.

Both are unbalanced types of cells. "A" cells are the superactive cancer cells in which condensed chromosomes with excessive timonucleinic content have the tendency to divide too frequently and too quickly. "B" cells are the exhausted regressive cancer cells with lack of timonucleinic acid in the chromosomes that have lost the capacity of reproduction.

Their recognition and their distribution in a tumor tissue is therefore most significant for diagnostic purposes as well as for the estimation of the degree of aggressiveness of a tumor.

Cusmano of the Gynecological Department of the medical school of Parma has applied to human cancer tissue a simple acetic-carmine stain, originated by Barigozzi for the study of chromosomes in *Drosophila*, and the result was the demonstration of the morphologic characteristics of the metabolic variations seen by Santesson and Caspersson under ultraviolet light, with a simple method that can easily be applied in routine clinical investigations. According to Barigozzi's technique, the material is fixed in acetic acid-alcohol, crushed under cover-glass, and stained with acetic-carmine. The cytoplasm is dissolved and only the naked nuclei are apparent.

"A" cells show a perfectly regular nuclear membrane and numerous small intensely red stained granules, representing the chromosomal chromomeres with high timonucleinic content, and among them one or two larger, faintly stained vesicular bodies that represent the nucleoli.

"B" cells show an irregular nuclear membrane, few faintly stained chromomeres, with low timonucleinic content and two clumpy, deeply stained central bodies representing the hypertrophic nucleoli with an excess of stored ribonucleinic acid that has lost the capacity to be transformed so as to provide the chromosomes with the amount of timonucleinic acid necessary for reproduction.

Using the above carmine-acetic method, Cusmano studied the distribution of "A" and "B" cells and the aspect and frequency of typical and atypical mitosis in cancers of the

cervix and fundus, the nuclear structure of hydatidiform moles and of chorionepitheliomas and he also applied the method to the investigation of nuclear features in vaginal smears. The results of these observations are most significant and are reported in the following abstracts.

GEMMA BARZILAI.

Cusmano, L.: Neoplastic Nuclear Features in Vaginal Smears Under Carminacetic Stain, Quaderni di Clinica Ostetrica e Ginecologia 2: 661, 1997.

After a painstaking review of American contribution in the field of detection of genital malignancy by the use of vaginal smears, Cusmano reports a modification of his own carminacetic method for cytologic investigations as a new approach to identification of the exfoliated tumor cells in the vaginal secretion.

For the preparation of the smear, vaginal content is secured with a pipette as described in the original Papanicolaou procedure. The material is immediately diluted with a generous amount of 1:2 acetic acid—alcohol mixture, and then centrifuged. Then the fixative is disposed of. Acetic-carmin is added to the vaginal sedimentation material which is then crushed under a cover glass, dehydrated in alcohol, and mounted on a slide.

Smears prepared with the technique described above in cases of neoplasms of the female genitals and examined at a magnification twelve hundred times show:

1. Nuclei with a regular nuclear membrane, containing numerous small intensely red colored granules disposed at regular intervals and definitely recalling in their aspect chromomeres connected by the colorless linin in the uncoiled chromosomes, thus representing the proliferative "A" type of neoplastic cells described by Cusmano and Barigozzi in former papers.

2. Nuclei showing an irregular but intact membrane and containing one or two large, clumped, deeply stained nucleoli and indistinct chromomeres.

3. Intermediate forms linking the two above types one to another and showing a few rather distinct chromomeres usually dislocated toward the nuclear membrane and large clumped but faintly stained nucleoli.

Among these nuclei, which are always largely represented in the smears when a cancer of the uterus is present and which are interpreted by Cusmano as cancer cells at rest, a few typical and atypical mitotic figures in the varied phases of reproduction are usually seen.

Small connective-tissue cells and large histiocytes are always interspersed among the epithelial cells. The histiocytes appear faintly and uniformly stained and it is not hard to distinguish them from the regressive epithelial cells at rest which are morphologically somewhat alike.

Cusmano's cytologic approach to cancer diagnosis in vaginal smears is established on sound objective criteria. It may well prove a milestone in the pioneering work which still has to be done in the development of the method of isolated cells in secretions and body fluids, a method of investigation that, as Warren says, is "as old as cellular pathology but that has started being successful only with Papanicolaou's work in the past decade or so."

GEMMA BARZILAI.

Gynecologic Operations

Darner, C. B.: Surgical Sterilization in Women, The Journal-Lancet 68: 118, 1948.

Pregnancy may follow Fallopian tube ligation if the suture material cuts through the tube and recanalization occurs. Nonabsorbable suture material permits this, and the author therefore recommends the use of catgut in the Pomeroy operation, No. 2 plain catgut being preferred because it induces more tissue reaction. In 141 cases sterilized by this method, there has been no failure. In cases of failure, the surgeon is not guilty of malpractice if "reasonable diligence" is exercised.

Without a medical indication, consent may be invalid because it undertakes to authorize an act contrary to public policy. Parity of four or more is considered an adequate medical

indication for sterilization, because the incidence of complications rises sharply after a fourth childbirth. This was the author's indication in one-half of the total series of 238 cases, the others being performed in the presence of various organic diseases. IRVING L. FRANK.

Macaggi, G. B.: Lying on the Abdomen in the Aftercare of Surgical Interventions for Vesicovaginal Fistulas, *Archivio Italiano di Urologia* 22: 114, 1947.

Keeping the bladder empty during the process of cure, or, in other words, avoiding infiltration of urine in the site of the reconstructed vesical wall, is the main problem of the post-operative care of vesicovaginal fistulas.

Urine infiltration never occurs after suprapubic incision of the bladder where the position of the lesion is such that urine does not come in contact with it. This lesion always heals spontaneously by granulation after the catheter is removed.

Keeping the patient lying on the abdomen while a retained catheter is in place avoids contact of the urine with the lesion, thereby creating a condition favorable for healing as in the case of suprapubic incision.

Macaggi used the "belly position" (which is accepted as a routine position in Italy) in two cases of fistulas that had been previously repeatedly operated upon without success.

Both cases healed: one by first intention and the other by granulations. The latter, quite an unusual event, should be borne in mind in cases of fistulas stubbornly resisting surgical treatment. According to the author, the "belly position" is to be credited for this success. GEMMA BARZILAI.

Dellepiane, G.: A Vaginal Technique for the Combined Treatment of the Prolapsed and Retrodisplaced Uterus, *La Ginecologia-Scritti in onore del Prof. Ercole Cova*.

Dellepiane, Director of the Lying-in Hospital and Medical School in Parma, describes a vaginal technique for the combined treatment of the prolapsed and retrodisplaced uterus in which a new step is added to a procedure that in the main corresponds to the operation generally known in this country as the Manchester operation.

A survey of operations heretofore described for the treatment of the prolapsed uterus is given, the contribution of the Italian school on this argument is stressed and credit is given to Pestalozza for focusing, as early as in 1902, attention on the significance of the shortening of the broad ligaments for the elevation of the uterus.

Dellepiane's operation consists of the following steps:

1. A "Y" incision is made in the anterior vaginal wall with the wide base slightly below the level of the inner os of the cervix and the other end about 1 cm. above the opening of the urethra. This is combined with a triangular incision in the upper and posterior vaginal wall with the apex at the cul-de-sac and the wide base at the same level as the anterior incision, thus marking the boundaries for a wedge-shaped amputation of the cervix.

The vaginal wall is separated from the pubic fascia. The bladder is separated from the pubic fascia and from the uterus until the vesicovaginal pouch is reached. Separation is then extended laterally and the broad ligaments are exposed. The cervical vessels are tied. Ureter slings are occasionally visualized. The bladder is pushed off. The uteropubic fascia is trimmed, or duplicated, and sutures are placed, catching the uterus only in the upper part. The cervix is not amputated at this step to avoid useless bleeding. This step takes care of the cystocele.

2. A triangular incision is now made in the posterior vaginal wall with the wide base at the perineum and its apex pointing to and almost touching the lower end of the above-described incision in the upper part of the posterior vaginal wall, a technical detail which permits an easy approach to sacrouterine ligaments.

The rectopubic fascia is severed and uterine insertion of the sacrouterine ligament is reached by gauze dissection on either side. Separation is extended laterally and downward and levator muscles covered by their fascia are visualized. Strong silk sutures are passed

correct fastening of the pivotal area of the uterus in the posterior part of the pelvis which draws the cervix backward and throws the fundus forward, thus correcting the retrodisplacement.

A wedge-shaped amputation of the cervix is now performed according to the previously assigned boundaries. The broad ligaments are duplicated and fastened at the isthmic stump. The cervix is rebuilt with vaginal wall tissue. The result of this step is elevation of the uterus and shortening of the cervix.

3. The rectovaginal fascia is now sutured. Vaginal walls are closed as in routine posterior colporrhaphy. This step, together with the levator suture, takes care of the rectocele, if existent, and of relaxation of the pelvic floor.

This operation has been carried on by Dellepiane for the past ten years. It has proved effective and does not interfere with pregnancy, or parturition. GEMMA BARZILAI.

Miscellaneous

Kent, C. F.: *Urine Versus Blood Serum in Friedman's Test for Pregnancy*, J. Missouri M. A. 45: 275, 1948.

There is considerable chance for error in the use of urine for making the Friedman test for pregnancy in ambulatory patients. Frequent causes of error are that: the patient may drink water after midnight, resulting in dilution of the hormone in the morning fasting specimen; there may be delay in taking the specimen to the laboratory, resulting in the dissipation of the hormone present and excessive bacterial growth; containers may be used that have previously contained other substances which cause the death of the test animal and necessitate a repetition of the test. When blood serum is used for the test, the blood is withdrawn at the laboratory and the serum used is freshly prepared in suitable containers; the blood specimen can be taken at any time of day, as the ingestion of fluid in ordinary amounts does not dilute the blood. In a study of 156 Friedman tests at one laboratory, it was found that in 81 urine tests, there were 33 positive (40.7 per cent) and in 75 blood serum tests, 41 positive (54.6 per cent). False positives are rarely a problem; it is false negatives that are of most importance. If errors in the collection of urine specimens could be entirely eliminated, the results of the two tests would probably be in agreement, but this is rarely possible in the average laboratory dealing with ambulatory patients. HARVEY B. MATTHEWS.

Anderson, C. D., and Seldon, T. H.: *Influence of Sex of Donors on Transfusion Reactions*, Proc. Staff Meet., Mayo Clin. 23: 149, 1948.

Hustin and Remy reported in the *Presse medicale* that in 80 reactions occurring in 864 transfusions, the incidence of reactions was higher when a woman was the donor; the highest incidence was observed when the blood of a woman donor was given to a woman recipient.

A review of the transfusions done at the Mayo Clinic in the first half of 1947 shows that in 2720 transfusions there were 139 reactions, an incidence of 5.1 per cent. With female donors the incidence of reactions was 5.7 per cent and with male donors, 4.6 per cent. While this difference in the incidence of reactions was small, considered in relation to the number of reactions, the rate was nearly 25 per cent higher with female than with male donors. With women recipients, the incidence of reactions was 5.8 per cent when a woman was the donor and 4.6 per cent when a man was the donor. With male recipients, the incidence of reactions was 5.6 per cent with a woman donor and 4.8 per cent with a man donor. These findings agree with those of Hustin and Remy, but do not indicate as great a difference between men and women donors as these authors report.

It is concluded that the sex factor is of no practical importance in blood transfusion, although the chances that a reaction will occur are somewhat higher when a woman is the donor. HARVEY B. MATTHEWS.

Goldzieher, Joseph S.: *A New Colorimetric Method for the Determination of Pregnandiol*, J. Lab. & Clin. Med. 33: 251, 1948.

A new method for the colorimetric determination of pregnandiol is described and its advantage over the Tálbot sulfuric acid technique discussed. The accuracy of this new

method is said approximately to equal the sulfuric acid one and greater stability of color is claimed. The colorimetric reaction is based on the interaction of pregnandiol with acetyl chloride and zinc chlorido in glacial acetic acid solution. S. B. GUSBERG.

Newborn

Wiener, Alexander S., and Gordon, Eve B.: Studies on the Conglutination Test in Erythroblastosis Fetalis, *J. Lab. & Clin. Med.* 33: 181, 1948.

The authors have studied comparatively a number of methods used for the detection of blocking ("univalent") antibodies; in the small group of cases presented, they have demonstrated the greatest sensitivity to result from the use of an albumin-plasma testing mixture, and they call this the albumin-plasma conglutination test. These studies suggest that the placental barrier readily permits the passage of this antibody, so that a good correlation between the maternal blocking antibody titer and the severity of the infant's erythroblastotic disease exists. This correlation does not appear to hold in the case of anti-Rh antibodies ("bivalent") whose passage through the placental barrier is more difficult, possibly depending on factors other than height of titer. S. B. GUSBERG.

Mollison, P. L.: Physiological Jaundice of the Newborn, *Lancet* p. 513, April 3, 1948.

Studies on the survival of placental blood erythrocytes and of adult erythrocytes when introduced into the infant blood stream indicate that the breakdown rate of the infant's own red cells is twice that of adult red cells. This rate is independent of the degree of polycythemia present. The increased hemolysis probably depends on rapid destruction of immature types of erythrocytes present at birth, the bulk of the cells behaving like adult cells.

While bilirubin liberation is three times that in the adult blood stream, this rate could not produce the high bilirubin accumulation of clinical jaundice if the infant liver could excrete maturely. Bromsulfalein excretion in infants is retarded and jaundiced infants have reduced amounts of bile pigment in stool and urine. It is therefore reasoned that although increased hemolysis is present, the chief cause of physiologic jaundice of the newborn is a poor excretory capacity of the liver. IRVING L. FRANK.

Wiener, A. S., and Brancate, G. J.: Erythroblastosis Fetalis Caused by Double Sensitization to the Factors rh" and Hr', *Anesthesiology* 9: 175, 1948.

In some cases, an Rh-positive mother has given birth to an erythroblastotic infant; such cases are due to some unusual type of sensitization. Some of these cases have been traced to sensitization to the A and B factors, but others can be explained only on the basis of the so-called Rh-Hr blood types. As is now recognized, there are at least three Rh factors, Rh₀, rh', and rh". The Rh₀ factor which is the original Rh factor is the most antigenic of these three factors. Blood of type rh does not contain Rh₀ factor, but it does contain at least two Hr factors, which are also present in most Rh-positive bloods.

In the case reported, the mother was Rh-positive and had five children living and well; the sixth child developed icterus gravis a few hours after birth; the child, as well as the mother, was found to be Rh positive. Complete blood grouping and Rh-Hr tests of the infant, when seven days old, and of the entire family showed all members of the family to be Rh-positive. The mother belonged to subtype Rh₁ Rh₁, and the infant to subtype Rh₁ Rh₂, thus showing the factor rh" that was not present in the mother's blood. The mother also was Hr' negative, while the infant's blood contained Hr'. Tests on the maternal serum indicated that the mother was doubly sensitized to both rh" and Hr' factors. If it had been possible to determine that this type of sensitization was present prior to the birth of the infant, the child could have been treated by a complete exchange transfusion from a donor of group AB, and Rh₁ Rh₁ subtype. Cases of Hr sensitization are very rare, and the serum for testing is not generally available. Transfusions of Rh-negative blood had been given before these

blood studies were made; further transfusions from a type A B, Rh₁ donor supposedly Hr-negative were given, but this caused deepening of the jaundice, and it was found that no tests had been made for the Hr factor. The jaundice subsided and the infant survived, but examination at the age of six months showed definite evidence of permanent brain damage.

This case gives additional evidence of the importance of the constitution of the patient in iso-immunization. Only about one in fifteen Rh-negative individuals becomes sensitized to the Rh factor under the natural conditions in which only a minute amount of fetal blood enters the maternal circulation, so that only constitutionally predisposed women become sensitized. In the case reported, the mother was evidently constitutionally predisposed to iso-sensitization, as she showed sensitization not only to one, but to two factors present in the infant's blood and not in her own blood.

HARVEY B. MATTHEWS.

Pregnancy, Complications

Burnett, C. W. F.: Suprarenal Haemorrhage and Pregnancy, Brit. M. J., p. 249, Feb. 14, 1948.

The author reports a case of massive suprarenal hemorrhage occurring in a 33-year-old gravida v, para i, who had had three abortions. She had been treated for a threatened abortion at two months and discharged in satisfactory condition. One month later, she was readmitted in vascular collapse, two hours after a spontaneous abortion. She died twenty minutes after admission. Autopsy showed bilateral massive hemorrhage of both adrenal glands.

The author briefly summarizes the three other reported cases in the literature, two of which occurred during pregnancy. The third occurred during the puerperium of a full-term pregnancy which had been complicated by mild pre-eclampsia.

The author challenges the opinion stated in the literature that massive suprarenal hemorrhage is associated with involutional changes in the adrenal glands. He feels the four cases now reported fail to provide sufficient evidence to substantiate this conclusion.

R. G. DOUGLAS.

Ogden, J. Kenworthy: Retroperitoneal Haemorrhage in Pregnancy, Brit. M. J., p. 389, Feb. 28, 1948.

The author reports in this article a case of massive retroperitoneal hemorrhage in pregnancy. A review of the six cases in the literature is given. The patient was a 25-year-old gravida ii, para i, who had delivered by breech delivery a 3,600 Gm. infant after a labor of thirty-six hours. The infant subsequently died of cerebral hemorrhage. The patient's antenatal course had been normal until approximately the thirty-six week, at which time she developed severe hypogastric pain followed by three convulsions and shock. The uterus became tense and tender. The case was considered to be antepartum eclampsia with premature separation of the placenta. The patient responded to antishock therapy, only to sustain a second episode of pain and shock twenty-four hours later. A classical cesarean section was performed and a macerated fetus delivered, there being a large retroplacental hematoma. Her immediate postoperative course was satisfactory. On the fourth postoperative day, she had a convulsion, went into a state of collapse, and died two hours later.

Postmortem examination revealed 2,250 c.c. of blood in the peritoneal cavity and a large retroperitoneal hematoma in the region of the pancreas and curvature of the duodenum. The exact site of the hemorrhage could not be determined.

The author's review of the literature reveals six previous cases, and five deaths. The deaths all occurred in cases in which the hemorrhage was in the region of the floor of the lesser peritoneal sac. The site of hemorrhage in the case surviving was in the pelvis. The fact that the author's case, as well as two previously reported, occurred in association with toxemia of pregnancy is pointed out. The author raises the question of the possibility of thrombotic processes in larger caliber vessels, such as is seen in the small vessels in eclampsia, and their being responsible for the hematoma in fifteen later cases.

R. G. DOUGLAS.

Canna, S.: The Initial Nervous Syndrome in Wartime Pregnancies, *La Ginecologia* 13: 497, 1947.

Vomiting, marked irritability, insomnia, considered by Canna as the characteristic syndrome of severe cases of initial nervous impairments in pregnancy, showed a marked decrease during wartime and the number of pregnant women showing no nervous disturbances during the first months increased remarkably.

The rate of severe nervous syndrome cases decreased from 20 per cent prewar to 6 per cent during the war; and conversely, cases of expectant mothers who showed no nervous impairment increased to 35 per cent, as compared with 25 per cent before the war.

This decrease of nervous symptoms during the war was not influenced by social or economic factors. It affected equally factory worker, farmer, and housewife.

Canna credits this remarkable reduction in nervous symptoms in the initial stage of pregnancy during the war to the reduction in fat and animal protein in nutrition. The psychological factor might have played an important role. GEMMA BARZILAI.

Radiation

Wells, J. J., and Popp, W. C.: The Use of Pyridoxine Hydrochloride in the Treatment of Radiation Sickness, *Proc. Staff Meet., Mayo Clin.* 22: 482, 1947.

The use of pyridoxine hydrochloride (vitamin B₆), given intravenously in the treatment of radiation sickness in 200 patients undergoing intensive roentgen-ray therapy, is reported. Twenty-seven of these patients were under treatment for carcinoma of the breast; fifteen for carcinoma of the cervix; six for carcinoma of the uterus; and nine for carcinoma of the ovary. This medication was given to patients who had nausea and vomiting during the course of radiation therapy, or to a few patients who had had radiation sickness during a previous course of treatment. The best results were obtained with a dose of 100 to 200 mg. given about half an hour before each roentgen treatment; the larger dose was used when treatment was given to the abdomen, thorax, or pelvis. In twelve cases of radiation sickness, placebo injections of sterile water were given; these placebos did not relieve symptoms in any case when substituted for the pyridoxine hydrochloride injections. In eighteen of the cases treated, results of the treatment were excellent; i.e., all symptoms of radiation sickness relieved; in 111 cases, results were good, nausea and vomiting relieved but some malaise persisting; in 52 cases, results were fair, nausea occurring occasionally; there was no relief of symptoms in 19 cases, 9.5 per cent. When radiation sickness was controlled, most patients were able to tolerate a heavier daily dosage of radiation, so that the duration of the treatment could be shortened. No toxic reactions or complications due to the administration of pyridoxine hydrochloride were noted in any case. The high percentage of favorable results in this series justified the continuance of pyridoxine hydrochloride in the treatment of radiation sickness. HARVEY B. MATTHEWS.

Erratum

In the article, "Normal and Cystic Structures of the Broad Ligament," by Drs. Gardner, Greene, and Peckham, issue of June, 1948, page 930, paragraph 2, third sentence, "it had undergone a *modern* amount of cystic dilatation," should read, "it had undergone a *moderate* amount of dilatation."

Correspondence

Structure of the Broad Ligament

To the Editor:

I have read with a great deal of interest Dr. Gardner's recent contribution on the structures of the broad ligament which appeared in the June issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*.

All will agree that eponymous nomenclature has many drawbacks, especially when applied to diseases and operations. In describing anatomic structures, however, proper names are often no more than localizations in the "geography" of the body and hardly more objectionable than proper names for cities or geographical areas. We could designate every spot on earth by its latitude and longitude but what a cold world that would make. Besides proper names in medicine do teach medical history.

I sympathize fully with Dr. Gardner's objection to the multiplicity of proper names but his attempt to reform nomenclature is a lost cause. We shall never be able to do without proper names unless we use tremendous circumlocutions. Witness, for example, the nomenclature of such fields as paleontology, ornithology, and botany.

There is, however, to my mind, a greater objection to Dr. Gardner's nomenclature in the present instance. He uses embryologic terminology for adult structures. The embryologist must use the terms mesonephric (really pronephric when it concerns the duct) and paramesonephric because when these systems develop the sex of the zygote is not yet determinable and the dominance of one or the other of the two duct systems in doubt. Certainly the Müllerian duct must be the "para" system, since it not only develops later but in some lower forms develops from the mesonephric tube. However, after the female sex of the fetus has been established, the oviduct is no more a paramesonephric duct than a living elephant is a paramastodon.

Another point, it is extremely hazardous to predicate histogenesis on histologic appearance. Even physiologic reaction is no safe criterion. (Moench: *Surg., Gynec. & Obst.* 49: 332, 1929.) Adenomyosis of celomic origin shows the same hormonal response as the eudometrium itself—and what of vicarious menstruation? Villi may develop on the peritoneal surface of the oviduct and it is immaterial whether they grow out from the tube or develop from the peritoneum (Moench, loc. cit.).

The "Müllerian" duct system is essentially a simple tubular affair but the mesonephric system is very complicated. Anyone who is familiar with the extreme rarity of true reduplications of the "Müllerian" ducts in the adult must be most reluctant to accept the numerous accessory oviducts which Dr. Gardner describes, even though it is certain that aberrant "Müllerian" tissue does occur in the broad ligament (Moench, loc. cit.).

Dr. Taylor has stressed the growth potentialities of the celomic epithelium. We find decidual reactions here and cell rests that simulate stratified squamous epithelium. May not, then, some of the accessory oviducts of Dr. Gardner be but celomic invaginations? While tubal diverticuli, when they reach the surface, acquire fimbriae, may not celomic invaginations do the same? Certain areas of the body seem destined to form a certain type of epithelium. I have seen a row of typical "Wolffian" duct cysts in the vagina, some of which were lined by squamous epithelium. Other cysts of the same origin contained blood. I have removed an epoophoron cyst which showed columnar epithelium and a few wartlike papillae (not villi) similar to those seen in serous cystadenomas of the ovary. It is difficult to assume that in this location of the broad ligament there should be accessory ovarian tissue. Tubules such as Dr. Gardner describes in the hilum of the ovary I cannot but regard as of mesonephric

origin regardless of the epithelial lining. It is difficult to assume anything else. A "Müllerian" duct branch in this location would have to be a tremendous structure comparatively unless we assume a phylogenetic atavism to such a form as salamander ater.

The pronephric duct becomes the mesonephric duct. The pronephros is an evanescent, small group of cells high in the abdomen. The mesonephros is much larger and extends lower. I personally believe that the "hydatid of Morgagni" is the unused, unabsorbed upper portion of the pronephric duct. That will explain its great frequency of occurrence. Were this structure paramesonephric, why has no one ever seen fimbriae surrounding its end? To say its end is closed is no explanation, it was open originally. The more mesially placed small cysts of the broad ligament seemed to stem, at least in the cases I have examined, from the epoophoron tubules.

In conclusion, I want to thank Dr. Gardner for a most interesting presentation, even if at present I cannot see eye to eye with him. Might I add that it is Keibel and Mall's Embryology, not Kiebel and Malls'.

G. L. MOENCH, M.D.

27 WEST 55 STREET,
NEW YORK, N. Y.
July 8, 1948.

Reply by Dr. Gardner

To the Editor:

We are pleased that Dr. Moench is in sympathy with our objection to the multiplicity of proper names for broad ligament structures and cysts; furthermore, we doubt that their usage is of notable importance even in the teaching of medical history.

He objects to the use of embryologic terms for structures found in the adult, yet the rete of the embryonic ovary is still called the rete in the adult ovary. Therefore, we fail to recognize consistency in his objection to the use of similar embryologic terms for persisting but nonfunctional structures in the adult ligament.

His proposal to use "paramesonephric" duct prior to the time of sexual differentiation and another term after the sex of the embryo can be recognized (even though the embryo is now only a few weeks older) would not add clarity to this subject. We doubt, though, that he really intended to use "oviduct" for this latter term (Paragraph 4, last sentence) since "oviduct" is an accepted term for a derivative of only a part of this duct; i.e., the uterine tube or oviduct.

We also are "familiar with the extreme rarity of true reduplication of the 'Müllerian' ducts in the adult." We presume Dr. Moench means true reduplication of the oviducts rather than "Müllerian" ducts, since this latter term should mean true reduplication of all derivations of the duct. However, we fail to see what the rarity of true reduplication of the oviducts has to do with the frequency of accessory oviducts. The formation of true reduplication of the oviducts represents a difficult and complex embryonic feat. The mechanism of formation of accessory oviducts is entirely dissimilar.

In addition, "the numerous accessory oviducts which Dr. Gardner describes" were specifically stated as being found in eleven of the 598 routine specimens, and in two of the eleven serially sectioned specimens. Perhaps our concept of the word "numerous" differs from that of Dr. Moench. Actually, however, the incidence is probably much higher than our data indicate, since routine sections would not necessarily include accessory oviducts. Perhaps we should emphasize that accessory oviducts are small, are not conspicuous, are recognized only when sought, are miniatures of the normal oviduct, and do not even approach in size and conspicuousness the "true reduplications" of the oviduct.

The remaining paragraph requires several comments:

"May then not some of the accessory oviducts of Dr. Gardner be but celomic invaginations?" If Dr. Moench means celomic invaginations in the embryo in or adjacent to the region of the primary ostium of the future oviduct, we agree. It is exactly the point we were trying to make in explaining the histogenesis of accessory oviducts. If he is referring

to "celomic" invaginations in the postembryonic or adult, we cannot agree. We grant the growth potentialities of this epithelium, and its probable importance in the formation of endometriosis, or endosalpingosis. Its ability to form a miniature replica of the oviduct with fimbria and well-differentiated inner and outer muscle layers seems unlikely.

We cannot follow Dr. Moench's logic in claiming that frequent occurrence of the hydatid of Morgagni is explained because it is derived from the "unused, unabsorbed upper portion of the pronephric duct." This belief would first necessitate evidence that this portion of the pronephric duct frequently persists. On the other hand, there is no doubt that a cranial remnant of the mesonephric duct (which we would prefer to call it rather than pronephric duct) may *rarely* persist. In one of our younger embryos we have observed such an isolated, semi-pedunculated cranial remnant. Dr. Moench may not have noted, but in our original report we stated that in an adult specimen, one of the pedunculated cysts in the region of the oviduct had simple cuboidal epithelium with a basement membrane and that we believed it to be a mesonephric duct remnant. This epithelium, by the way, is identical to that of the mesonephric duct found normally in the adult broad ligament. It is extremely difficult to believe that this hydatid, and the others which had epithelium identical to that of the endosalpinx, had a common single histogenesis.

G. H. GARDNER,
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CHICAGO
Oct. 13, 1948.

Necrology

Charles Russel Robbins, M.D., of Richmond, Va., Emeritus Professor of Gynecology at the Medical College of Virginia, died Oct. 16, 1948, at the age of 80 years. A graduate of the Medical College of Virginia in 1894, a founder and head of the Stuart Circle Hospital, member of various professional societies, surgeon of the Richmond Light Infantry in World War I, Dr. Robbins retired from active practice in 1946.

CASE 4.—Aged 53 years, para vii. Menopause two years previously, no bleeding since.

Small endocervical polyp with small area of erosion at the margin of the external os which bled easily on touch. Uterus normal size in third degree retroversion.

Polyp removed and vascular area biopsied. Cervical polyp was benign.

Cervical biopsy report: "Squamous cell metaplasia, carcinoma in situ" (Fig. 4). Slide was submitted to two pathologists in consultation. One diagnosed carcinoma of the cervix; the second, carcinoma in situ.

Subcervical and tandem application of radium for a total of 6,600 mg. hours was followed by deep x-ray therapy.

CASE 5.—Aged 38 years, para ii, gravida ii. Interval bleeding for one year.

Normal pelvic organs except for typical circumoral "erosion." Biopsy taken from the only area in erosion which bled on touch.

Biopsy report: "Diagnosis deferred. Equivocal lesion of the cervix. More tissue requested."

Biopsy of the cervix nine days after the original biopsy. Report: "Carcinoma in situ of cervix" (Figs. 5A and 5B).

Total hysterectomy, bilateral salpingectomy and oophorectomy. Dense pelvic adhesions of tubes and ovaries were found at operation.

Multiple sections of excised cervix showed *no carcinoma in situ*.

CASE 6.—Aged 31 years, para 0, gravida i. Menometrorrhagia one year. Last menstrual period three weeks previously. Previous bilateral salpingectomy.

Cervix negative in appearance with pin-point os. Uterus 180 degree anteflexed with fundus enlarged symmetrically twice normal size. Uterine cavity could not be entered due to the marked anteflexion. Endocervix was curetted.

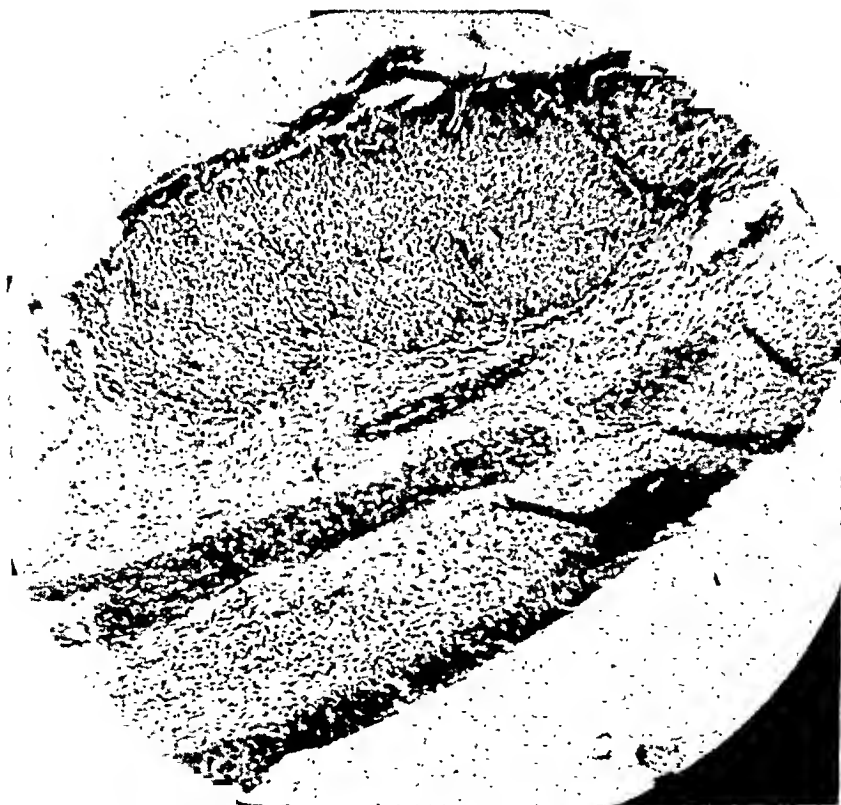


Fig. 4.—Single nest of atypical cells in the endocervix. Membrane prominent with no evidence of invasion. ($\times 50$.)

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Diagnosis: "Endocervix showing squamous cell metaplasia." Slide reviewed four weeks later at request of resident pathologist. Diagnosis amended: "Squamous cell carcinoma of the cervix, Grade II."

Consultant (pathologist) disagreed. Diagnosis: "Metaplasia."

Endocervix again curetted three days later. Diagnosis: "Cervix showing squamous cell metaplasia."

Total hysterectomy and right oophorectomy performed, left ovary conserved. Original section of excised cervix showed only metaplasia (Fig. 6A). Cervix recut and section reported: "Squamous cell carcinoma, Grade 2" (Fig. 6B). Following the establishment of the diagnosis of invasive carcinoma of the cervix, deep x-ray therapy was instituted.

CASE 7.—Aged 42 years, para ix. Menorrhagia three months. Cervix showed elevated avascular area at the margin of the external os subsequently shown to be a deep retention cyst. An applicator introduced into the cervical canal was blood tinged. Remainder of pelvic organs normal. Curettement of endocervix performed.

Biopsy report: (Endocervical curettings.) "Squamous cell carcinoma of the cervix" (Fig. 7A). Further tissue requested to differentiate between intraepithelial and invasive carcinoma. Scalpel conization performed. Original section showed intraepithelial carcinoma (Fig. 7B). Recut of block showed definite invasive carcinoma.

We wish to thank Dr. Ferdinand C. Helwig for the help and advice he has given us in the preparation of this paper.

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Discussion

DR. HERBERT E. SCHMITZ, Chicago.—The presentation of Drs. Cox, Buhler, and Mixson is timely and should serve as a stimulus to the members of this society to emulate their procedure. We have for years proposed routine biopsy of all cervical lesions irrespective of their clinical appearance, claiming that the microscope was the only adequate method of diagnosing early cancer. A biopsy forceps and bottle of fixative should be found on every gynecologist's instrument table next to the vaginal speculum. Just what changes we may interpret as cancer are still debatable and some of us choose to err on the radical side rather than to sacrifice a life by our attempt to be ultraconservative. If doubt exists, repeat biopsy, conization, amputation of the cervix or vaginal hysterectomy with conservation of the ovaries is indicated.

Cases 1 and 2 in this series demonstrate the great difficulty in properly interpreting lesions occurring in the cervix during pregnancy. Further studies of the cervical changes occurring during pregnancy are needed. In Cases 3 and 4 the diagnosis seems quite evident, and total hysterectomy with conservation of the ovary in the younger woman the method of choice. In Case 4 either removal of the uterus and the adnexa or irradiation would suffice. The same would hold for Case 5. Cases 6 and 7 illustrate the need of careful recheck of all doubtful cases so that incomplete treatment is not carried out. A registry such as the essayists advocate will be of great value in giving others an opportunity to review questionable microscopic sections and thus improve their own diagnostic ability.

Early diagnosis of cervical cancer offers the greatest weapon in the successful treatment of this condition. Through lay education we are seeing the patient at a time when careful examination of the genital tract is necessary. If we overlook a serious lesion and reassure our patient falsely we send her to her doom. May I again appeal to the members of this society to follow in the footsteps of Dr. Cox and his co-workers.

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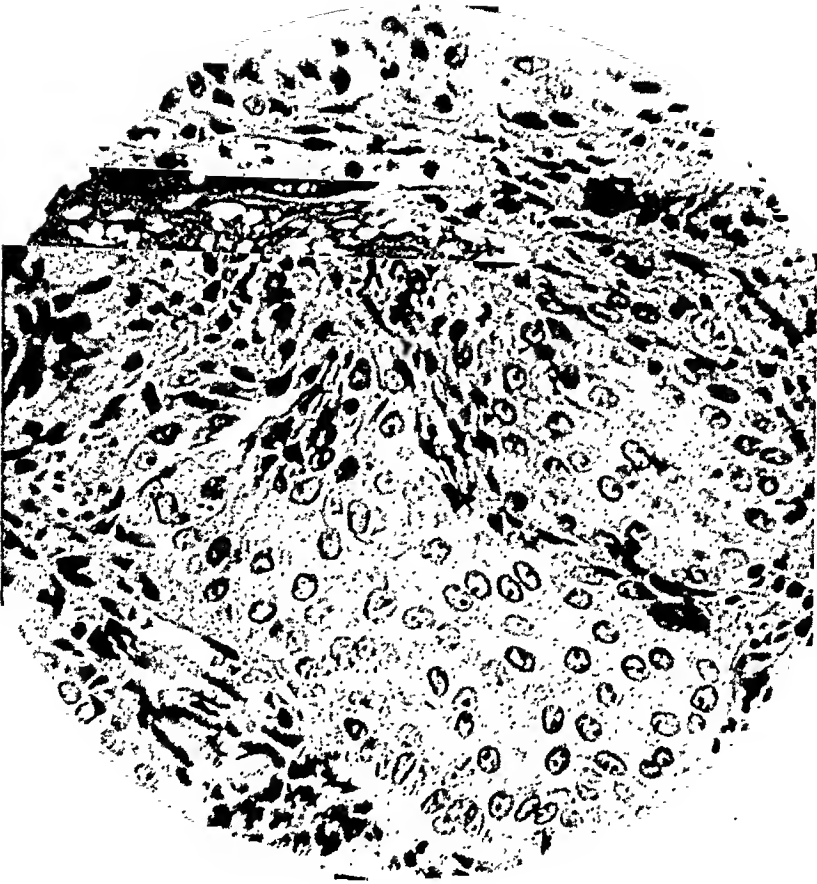


Fig. 6A.—Area of squamous cell metaplasia noted in first block of tissue from cervix removed at panhysterectomy. Lesion considered benign. ($\times 215$.)



Fig. 6B.—Section taken from further block cut from cervix removed showing definite invasive carcinoma. ($\times 50$.)



Fig. 5A.—Area of intraepithelial carcinoma. Note well defined basement membrane. ($\times 1$)

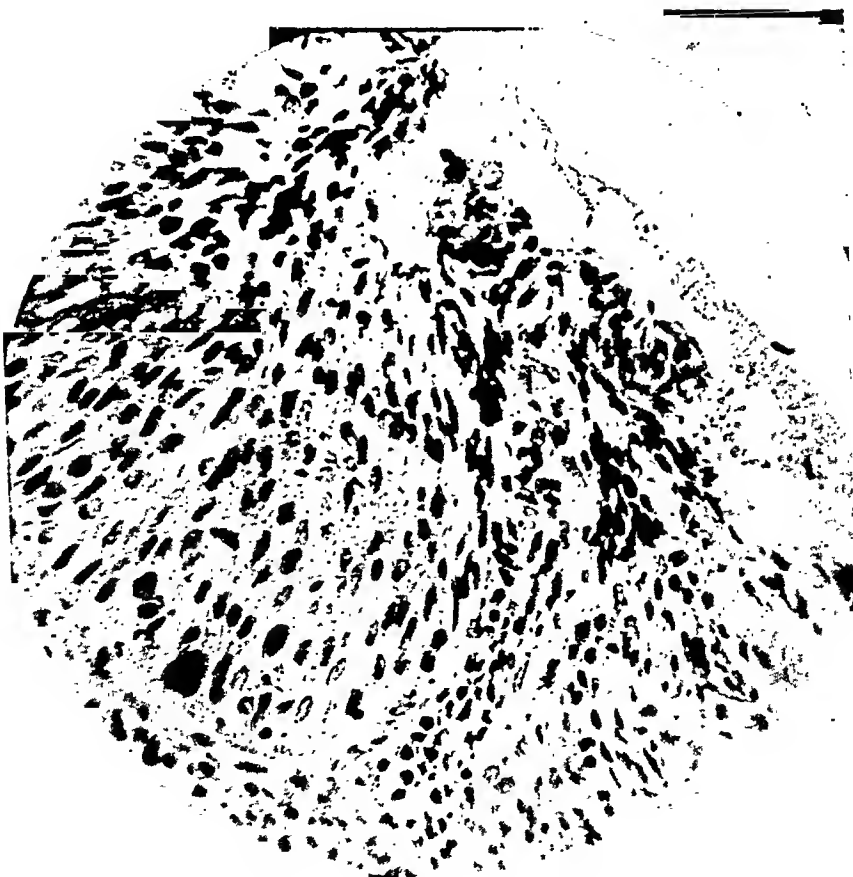


Fig. 5B.—High power magnification to show cell type. ($\times 215$.)

DR. JOHN HUFFMAN, Chicago.—Dr. Arthur Curtis has long emphasized that the diagnostic removal of a piece of tissue from the cervix for the diagnosis of early cancer is not the procedure of choice. Instead, wide removal of all unhealthy tissue from a suspicious cervix is to be preferred. If necessary the unhealthy cervix should be amputated. Such an amputation will not only obtain sufficient material for adequate study but will remove diseased tissue which would have been a potential danger in the future. Needless to say, when a suspicion of malignancy has been raised, many blocks should be taken and many sections cut from each block. Dr. Cox's report has emphasized the necessity for adequate training at our teaching centers of young men in gynecologic pathology. It is an indispensable part of the residential training of the gynecologist and until we have adequate pathological material for our residents and junior staff we will not produce competent gynecologists. We have all had the experience of equivocal reports from general pathologists. Until we cut our own "blocks" and, until we train our young men to interpret adequately their own tissue specimens, we will continue to have difficulties.

DR. COX (closing).—I appreciate Dr. Schmitz's remarks concerning vaginal smears. We did not mention these because we do not know much about them. The problem of the diagnosis in these extremely early lesions is still a matter of interpretation of cancer cells in the tissue itself, requiring training and experience to enable one to diagnose such cells when isolated on a smear, and that is beyond us at present.

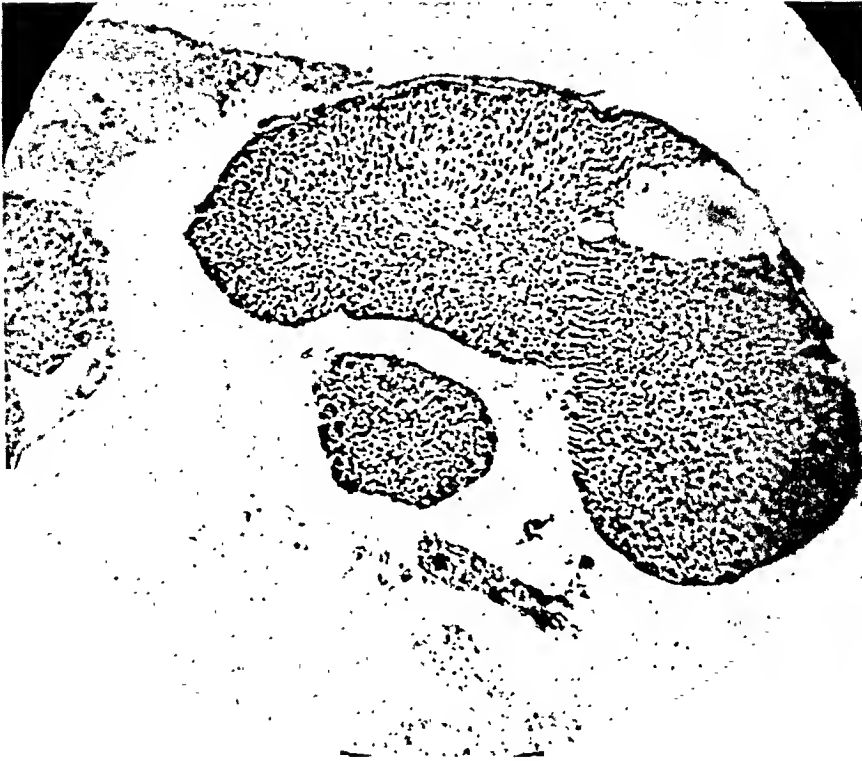


Fig. 7A.—Tissue removed at curettage of internal os. Definite neoplastic nature of the cells established. Absence of supporting tissue makes differentiation between intraepithelial and invasive carcinoma impossible. ($\times 50$.)

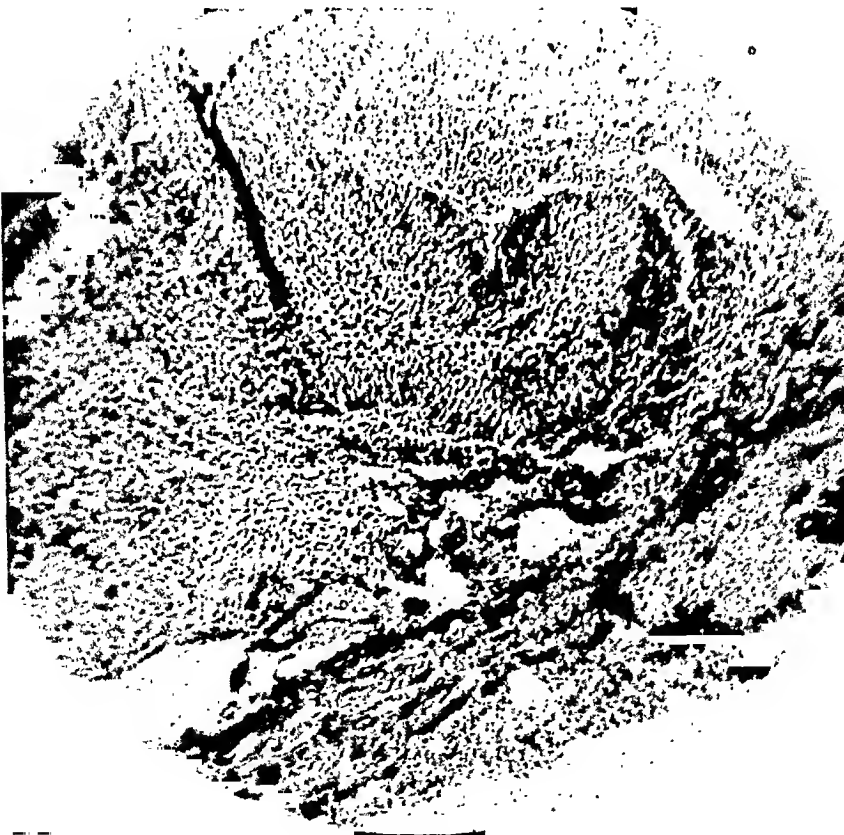


Fig. 7B.—Nest of well delineated neoplastic cells demonstrated in the first section taken from tissue removed by scalpel conization. ($\times 50$.)

applicator a sound was elicited much like that produced when a small rubber balloon is pinched between the fingers. It was immediately evident that the cystoid spaces contained a gas rather than the usual mucus of nabothian cysts. Some of the larger lesions were punctured with a sharp-pointed scalpel and only gas escaped, there being no exudate nor secretion of any type. The gas-filled spaces were discrete and independent, each failing to lose its gas, and thus its contour, when neighboring cavities were punctured. That these spaces had no communication with each other was further shown by minute examination of excised wedges of the cervix subsequently removed. Firm palpation produced no crepitation as would be expected in true emphysema. The gas-filled cavities projected slightly above the general contour of the cervix. The epithelium covering the larger vesicles was thin and translucent. The lesions were so numerous that only patches of normal appearing cervical mucosa were present. The mucosa of the vagina was normal and there was no unusual discharge.

Repeated wet smear examinations of the vaginal secretions showed no trichomonads. Repeated vaginal smears stained by Gram's method showed gram-negative cocci predominating. No *Monilia albicans* nor other type of fungus was seen on stained smears, and there was no growth on Sabouraud's. The vaginal secretions tested with nitrazine paper showed a pH of about 7. Bacterial cultures were made by incising the epithelium over the cystoid spaces and swabbing their interior with cotton tipped applicators. Plants on the following media showed no growth: brain heart infusion blood agar, aerobic and anaerobic; glucose heart infusion semisolid agar deeps; anaerobic agar (BBL); brain heart infusion broth and Sabouraud's.

Washings were obtained from the cystoid lesions by injecting and aspirating normal saline through a hypodermic needle. These washings (0.5 c.c.) were injected into the vaginal wall of a mature rabbit. Gross and microscopic examinations of the vaginal wall after seven days showed no evidence of gaseous lesions. Since a rabbit's vagina is not necessarily susceptible to the same diseases as a woman's vagina the test may bear no significance.

At seventeen weeks' gestation, with the patient under cyclopropane anesthesia, a generous wedge of tissue was removed from the cervix for pathologic study. The patient was frequently examined throughout her pregnancy but no marked changes in the cervix were discernible. At thirty eight weeks' gestation the patient developed a premature separation of the placenta with an estimated blood loss of 300 c.c. Labor ensued immediately. After three hours, spontaneous delivery of a normal six pound, two ounce male infant occurred.

Palpation and close inspection of the cervix following delivery showed clearly that the gaseous lesions were limited to the portio vaginalis. There was no evidence that any of the cystoid spaces had ruptured during labor and there were no lacerations. After delivery of the placenta two large wedges of cervix were excised (Fig. 1). Upon removal of these wedges of tissue it was apparent that the entire thickness of the cervix was involved, the organ being literally honeycombed with the gas-filled lesions. When these pieces of tissue were submerged in water they were noted to bob to the top with the rapidity of a fishing cork. When a cavity was punctured beneath water, bubbles of gas would escape and rise to the surface.

The patient's puerperium was entirely uneventful. Examination of the cervix on the fifth postpartum day showed many of the lesions present, but their size had markedly diminished. Examination of the patient on the fourteenth postpartum day showed only three or four small lesions remaining. These were on the posterior lip at the site of some previously very large cysts. Examination six weeks postpartum showed a cervix essentially normal, free from cysts of any kind and with no erosion.

Microscopic Findings

(Tissue taken at 17 weeks' gestation.) Sections of cervix reveal surface covered by mature stratified squamous epithelium with slight parakeratosis. The fibromuscular tissue contains in places numerous inflammatory cells, chiefly lymphocytes with occasional polymorphonuclear eosinophiles and polymorphonuclear neutrophils. A few macrophages

VAGINITIS EMPHYSEMATOSA*

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OF SUCH rarity is the condition variously known as vaginitis emphysematosa, colpohyperplasia cystica, and emphysematous colpitis, that it might well be placed within the realm of medical curiosities.

After encountering the condition and being totally ignorant of its nature, its characteristics were discussed with some forty obstetricians and gynecologists. None of these recalled having seen anything similar and only one expressed any knowledge of such a lesion. An assumption could then be made that the condition is comparatively unknown.

The lesion was first described by Hugier¹ in 1847 and subsequently by several German authors. The German literature of the nineteenth century contains a relatively large number of case reports. The combined literature of America and Great Britain contains the reports of only eleven authentic cases²⁻⁹ of vaginitis emphysematosa. Four other cases^{10, 11} might be included, but from the descriptions given there seems to be little similarity. Since the history of the lesion was well covered by Ingraham and Hall⁴ in 1934, further historical data will be omitted.

The characteristic lesion is one of gas-filled cystoid cavities of the mucosa and submucosa of the vagina and cervix. The lesion usually involves both the upper vagina and the cervix, but occasionally is limited to one site or the other. Vaginitis emphysematosa is more often seen during pregnancy. The condition is productive of only mild, if any, symptoms. The point of greatest interest concerns its etiology and this remains obscure. Although several theories have been formulated as to its development, none seem acceptable to our present-day pathologists with their increased knowledge of causes and pathogenesis of diseases.

Case Report

Mrs. M. C., white, aged 32 years, gravida iv, para ii, came under observation as a private patient on Aug. 19, 1946, at which time she was pregnant, being twelve weeks past her last menstrual period. She presented no symptoms except those of early pregnancy and her general physical examination showed nothing unusual. Blood examination showed red cell count 3,110,000; hemoglobin 8.2 Gm.; white count 8,900 with neutrophils 70, leucocytes 29, eosinophils 1; Kline and Kahn tests negative; Rh factor positive; sedimentation rate (Wintrobe) 17 mm. The urine was negative for sugar and albumin. Pelvic examination showed moderate relaxation of all pelvic supports; the uterus corresponded in size to that of a twelve-week pregnancy.

The lesion with which this presentation is concerned appeared on the cervix. The cervix was softer than the usual cervix in pregnancy, to the extent that it was difficult to outline by palpation. Speculum examination showed the cervix to have a bulk four or five times that of normal. This enlarged cervix was filled with, or almost replaced by, opalescent lesions resembling Nabothian cysts. The cysts were limited to the cervix and they varied in diameter from one to fifteen millimeters. When the cervix was wiped briskly with a cotton tipped

*Read before the Central Association of Obstetricians and Gynecologists on Oct. 24, 1947, in Louisville, Ky.

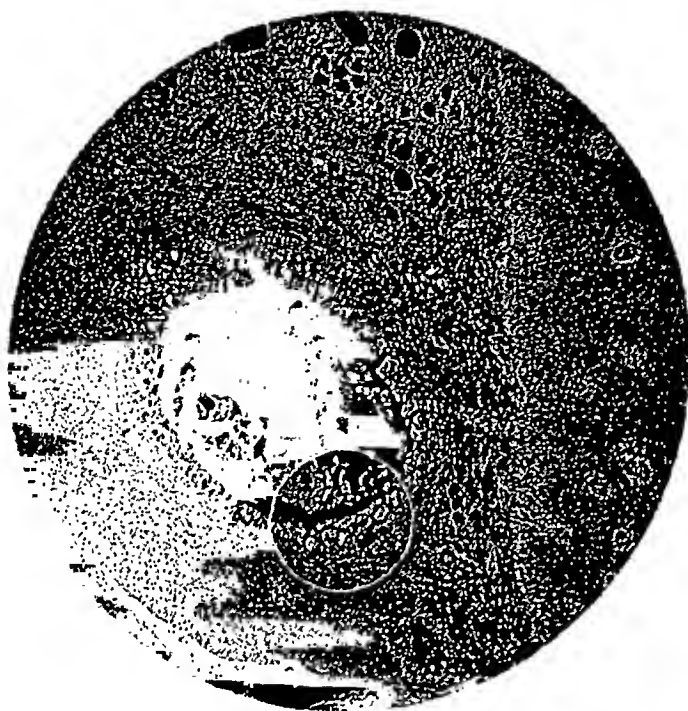


Fig. 3.—Low power of a very small gas-filled cavity lined with large undistorted multi-nucleated giant cells ($\times 65$).



Fig. 4.—High power from encircled area in Fig. 3. Giant cells are clearly shown. The red blood cells within the lumen are presumed to have resulted from trauma at the time of removal. Some giant cells have been shed into the lumen ($\times 250$).

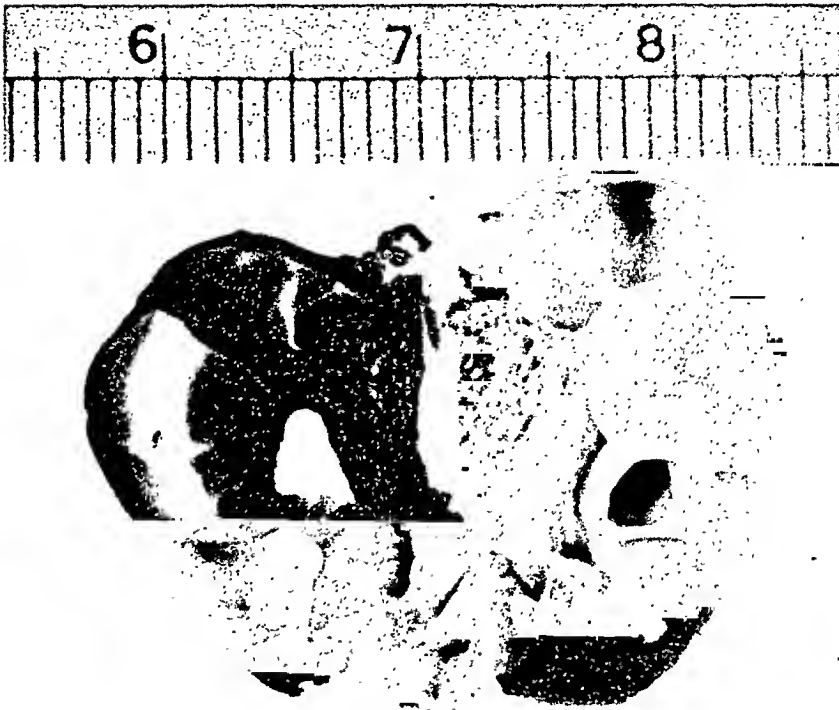


Fig. 1.— Gross appearance of cervical tissue removed at time of delivery. Incised and spread open. The centimeter rule indicates size of individual gas-filled cystoid locules.



Fig. 2.—Only thin partition separating some gas-filled cavities ($\times 15$).

determining the nature of the gas. They have shown that the gas is not pure oxygen, carbon dioxide, trimethylamine, nor hydrogen sulfide. Their work has indicated, and the assumption of others has been, that the gas could be air, but the volume of gas available has always been too small for accurate analysis.

I should like to present arguments opposing the idea that the gas is air. That air could be present in the vaginal canal under sufficient pressure to be forced into the cervical and vaginal tissues seems only remotely possible. Instead of having a true emphysema with a free movement of gas within the tissue spaces, with a characteristic crepitation on palpation, we have what appears to be totally independent gas-filled locules from which the gas is not displaceable. Since it is probable that there is a constant absorption into the blood stream of any gas within living tissues, it should be assumed that a continuous and endogenous source of gas does exist. If all evidence is correct that these numerous locules are discrete, the necessity would then be that each cavity must have its own source of gas for its maintenance, or for its increase in size as individual locules can be observed to do during an extended period of observation.

A more rational view would seem to be that the gas is other than air and that it has its origin within the tissues. Whether we are dealing with a rare form of degeneration or decomposition, a slow-growing, gas-forming microbe or some other unknown process, is a point obviously unsettled. Although the bacteriologist reported no growth on various aerobic and anaerobic culture media, and careful bacteriological investigation by others has failed to prove a bacterial cause, the idea should not be totally discarded. Slow-growing bacteria, offering difficult cultural problems, such as acid-fast bacilli frequently produce giant cells, and it is possible there is one capable of producing gas.

Concerning the giant cells partially lining many of the cystoid cavities, several authors have made the assumption that they have resulted from the gas acting as a foreign body. This view may be entirely correct but it does not fully explain the giant cells in the stroma outside of and away from gaseous cavities as appear in the case presented. That isolated groups of giant cells (Fig. 6) do exist would seem to indicate that they have not resulted from the gas acting as a foreign body, but rather that the gas and giant cells are elements of the same endogenous process.

Some possible stages in the development of this lesion are shown diagrammatically in Fig. 7. This idea was conceived by the author after much study of the microscopic sections.

Lesions similar, and probably analogous to vaginitis emphysematosa are cystitis emphysematosa of the urinary bladder and pneumatosis cystoides intestinalis. Since these lesions of unknown etiology affecting the urinary bladder and intestinal tract resemble vaginitis emphysematosa in so many respects, a logical assumption would be that the three have a related etiology.

Summary and Conclusion

1. A rare and interesting lesion has been called to the attention of the members of this society and a case report is being placed on record.

are present and contain blood pigment. The most striking finding is the presence of giant cells and cysts. The cysts vary in size from small microscopic structures to large ones where only a part of the wall can be included in a low-power field. The cysts appear to be empty. Lining these cysts are numerous giant cells, some of which project as oval or rounded multinucleated cells giving an irregular lining. These cells usually contain six to twelve nuclei which are round or oval. The cytoplasm is stained pink by eosin and is finely granular, nonvacuolated, and contains no demonstrable organisms. In part these cells are flattened as if compressed by pressure and have a syncytial appearance. Multinucleated giant cells are not confined to the immediate cyst wall but extend a short distance into the adjacent fibromuscular tissue of the cervix. A few clusters of these multinucleated giant cells of larger sizes are seen in inflammatory areas without cyst formation surrounded by numerous inflammatory cells, chiefly lymphocytes. In the immediate vicinity of the giant cells the tissues are loose, and numerous small spaces are formed by strands of loosely arranged tissue, and the impression is given that these are the early stages of cyst formation. No semblance of definite cyst wall has yet formed here. Occasional cysts near the surface are in part lined by mature stratified squamous epithelium. The blood vessels and lymphatics in these sections are prominent. A few are lined by swollen endothelium.

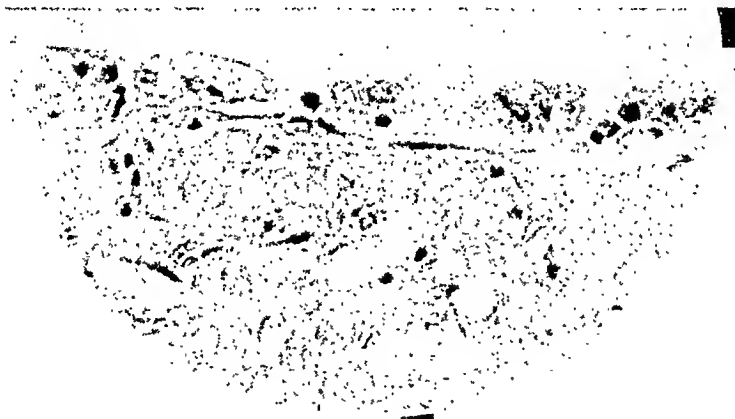


Fig. 5.—High power of a larger lesion showing giant cells partially flattened from intracystic pressure. Giant cells in most lesions are more compressed ($\times 400$).

Cervical tissue removed at time of delivery reveals on microscopic examination the following: Mild focal chronic inflammatory reaction and cysts. The inflammatory reaction consists principally of lymphocytes. The cysts are much larger than those seen in previous biopsy specimen. The very large cysts frequently lack specialized cells and appear to be lined by stretched out cervical stroma. In a few places are seen very thin syncytial type cells suggesting greatly compressed giant cells. A few less large cysts near the surface possess an almost intact syncytial type lining. There are present a few definite multinucleated giant cells, only moderately compressed and flattened. These, too, form part of the cyst lining. Some cysts are close together and have a thin common wall separating the cysts. The fibromuscular cervical tissue is loose and edematous. Moderately prominent blood vessels and lymphatic vessels are noted. Surface stratified squamous epithelium appears vacuolated and intercellular bridges are more prominent than usual. Gram's stain reveals no organisms. Fat stains reveal little fat present, there being none in the cystic cavity. A few giant cells contain multiple small droplets of well-stained fat but the vast majority contain no stainable fat.

Discussion

Neither the origin nor the chemistry of the gas contained within the cystoid spaces has been determined. Ingraham and Hall⁴ have given a complete review of the literature and they have described their attempts at

2. It is probable that the lesion is a pathologic entity but without great clinical significance.
3. The etiology of the lesion remains obscure.
4. There is little evidence that the lesion is productive of symptoms.
5. Argument is presented supporting an opinion that the gas within the lesions has an endogenous origin as opposed to an assumption that the gas is air.
6. Some possible stages in pathogenesis have been suggested.

The author expresses his sincere appreciation to Dr. Stuart A. Wallace, Department of Pathology, for the microscopic descriptions, and to Dr. Preston E. Harrison, Department of Bacteriology, for the bacteriological studies.

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Discussion

DR. CLARENCE INGRAHAM, Denver, Colo.—This is a most interesting and unusual condition. This patient mentioned a feeling of fullness and had been conscious at times of the rupture or bursting of a cyst, producing an audible noise, but being practically devoid of symptoms. As Dr. Gardner has said, the main interest lies in the determination of the method of formation of these cystoid cavities.

There are two similar lesions, analogous in some respects, occurring elsewhere in the body. With pneumatosis cystoides intestinalis, in this affection, gas-filled vesicles appear in the wall of the intestine, chiefly beneath the serosa of the ileum, but also of the colon. The other lesion, cystitis emphysematosa, described by Mills and others, shows vesicle formation in the bladder wall.

The same discussion arises concerning the etiology of these gas-filled vesicles as in emphysematous vaginitis. Is the gas derived from bacteria, or is air forced into the tissues through minute lesions by mechanical pressure?

I have had the opportunity of observing three cases of emphysematous vaginitis which occurred in the Colorado General Hospital, two were in pregnant women, the third in a patient from the Psychopathic Hospital, who died from strangulation with food and was autopsied eight hours later. This patient had a thin-walled hydrosalpinx on the right, the left tube was closed and thickened, the ovaries and uterus were grossly and microscopically normal. The vagina was studded with small cysts 1 to 3 mm. in diameter, many had broken down and coalesced to form small ulcers. The cysts contained gas under pressure and were microscopically similar to the two cases in the pregnant women. Cultures taken from the cysts remained sterile for three days, but on the fourth an aerobic spore bearing nongas-forming rod developed which we interpreted as an accidental contamination. There were no bacteria in the microscopic stained specimens made from the walls of the cysts.

In the two pregnant women, extensive examinations were carried out by Dr. Ivan C. Hall who was then head of the bacteriological department of the Colorado School of Medicine, and who is coauthor of the paper on emphysematous vaginitis, which we published in THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, November, 1934.

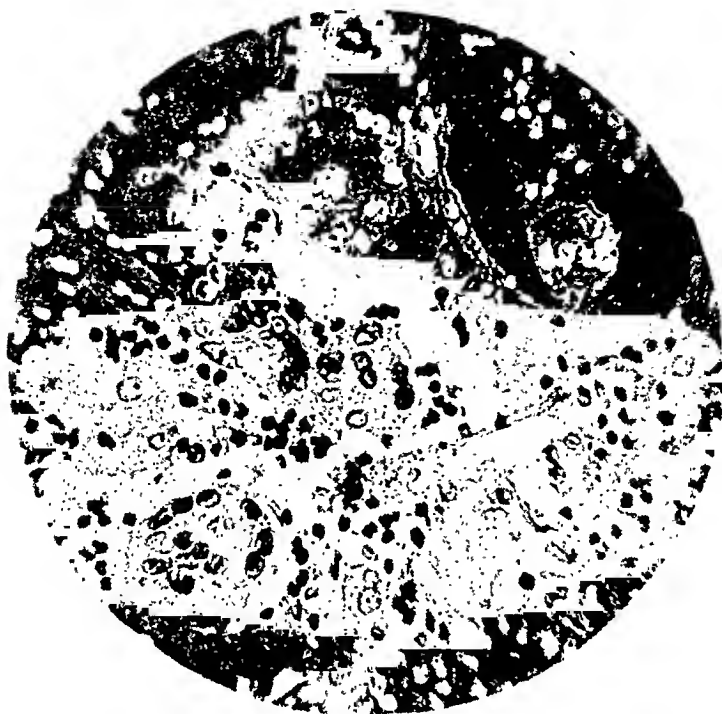


Fig. 6.—Isolated group of giant cells away from gas-filled cavity. Note loosely arranged stromal tissues. This possibly early stage of gas-filled cystoid lesion ($\times 400$).

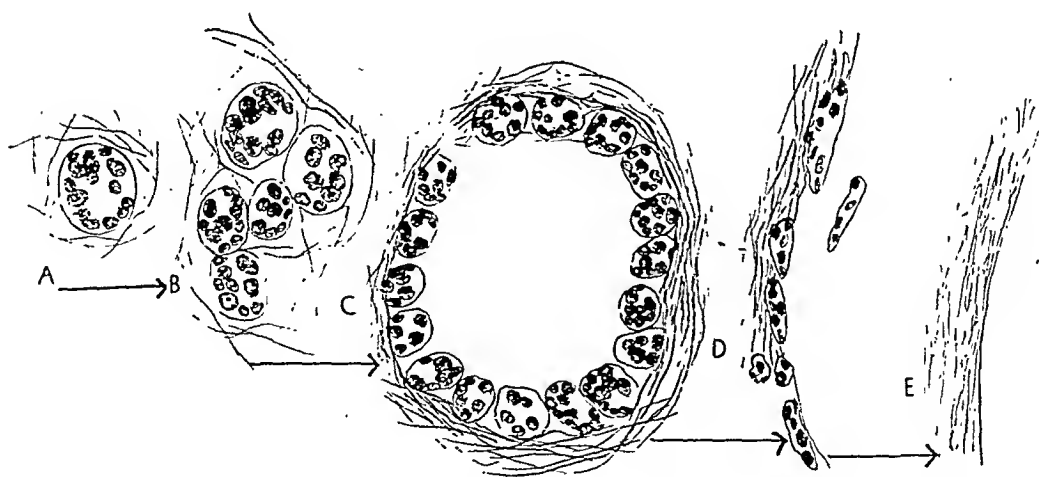


Fig. 7.—Some possible stages in pathogenesis: *A*, Giant cell. *B*, Group of giant cells. *C*, Small gas-filled cystoid lesion lined with large undistorted giant cells. *D*, Larger cystoid lesion with lining giant cells partially flattened from intraeystic pressure. Occasional giant cell detached. *E*, Largest lesions lined chiefly with stretched out cervical stroma, presumably the majority of the giant cells having been shed into the lumen, although an occasional very thin giant cell can usually be seen in the largest lesions.

Our second case shows no downward growths of epithelium but only cysts similar to those described by Dr. Gardner. Their walls consist of fibrous tissue, no epithelial or endothelial lining can be demonstrated. Many flattened giant cells remain along the walls partially lining the cavity, so compressed in certain areas that the nuclei lay in linear order. In the region of the vesicles there is slight infiltration with lymphocytes.

No bacteria were found excepting on the surface and in the most superficial layers of the epithelium.

The origin of the vesicles seem to be by distention of tissue spaces rather than dilation of lymphatic channels. The giant cells are to be considered of histiocytic origin presumably in response to the presence of gas acting as a foreign body. As Dr. Gardner has suggested, these spaces are not true cysts as they do not extend preformed glands or cavities but merely lie within temporary cavities in the interstices of the tissue.

The lack of any marked inflammatory reaction, the failure to recover any single species of microorganism repeatedly from the cysts themselves, the absence of bacteria in stained tissue slides with hematoxylin and eosin, Gram, Giemsa, or Loeffler's methylene blue, excepting on the surface and in the most superficial layers on the vaginal epithelium, our inability to reproduce the cysts in laboratory animals with vaginal secretions, or with any of the bacteria cultivated from the vaginas of these patients suggests that the process is nonmicrobic, and that if bacteria are concerned they do not belong to any of the readily cultivatable and easily recognizable species.

Since we have been unable to demonstrate anything but air in the cysts, we are confronted by the difficult problem of explaining its presence. No physiologic or microbic process is known that would result in the formation of air in the tissues.

It may be that air could be driven into tissue through epithelial defects or gain entrance by way of epithelial down growths which become liquefied, or entering through the cervical glands finds its way along the walls of the vagina. Any of these explanations would sound fantastic.

DR. MILTON A. DARLING, Detroit, Mich.—It happens that I have seen similar cases. The first time I reviewed the literature extensively and found no description of it whatever. I took care of this woman through two pregnancies and the condition appeared in both of them along the posterior vaginal wall, except that the growths were largely on the vagina and did not involve the cervix. Our second case was a nullipara in which the cystic areas largely involved the cervix and vault of the vagina and had no connection with the vaginal floor. The problem in this case was that the woman complained of pain during coitus. It was never determined whether this was the cause as she had other pelvic pathology which could have accounted for pain and discomfort of which she complained.

DR. GARDNER (Closing).—I am glad to hear that others in this audience have seen this condition and I would like to see the cases reported. Various and sundry explanations have been offered by some of the older authors as to how air becomes entrapped in the mucosa of the cervix and vagina. None of their explanations seem logical and I cannot subscribe to any of them. I do not believe that the gas is air and under no circumstances can I see how air could have been entrapped between folds of mucosa or forced into the cervical tissues in the case presented here.

Microscopic and cultural examinations were made from the vaginal fluids using the various media and staining materials. Nothing out of the ordinary was obtained except that in our first case a gram-negative vibrio was repeatedly and abundantly seen, but could not be cultivated. Cultural examinations were made of the gaseous cysts. The results were negative in all but one instance when an unidentified nongas-forming rod was recovered. These findings were interpreted as an indication that the cysts were actually sterile.

Several injections of vaginal fluid of both pure and mixed cultures and from the cysts' contents were made into the vaginal wall of rabbits and guinea pigs. In several instances there were marked inflammatory changes, with abscess production in one instance, but no lesions suggestive of emphysematous vaginitis.

The lesion being a harmless affection, on two occasions with permission, the vaginas of pregnant women were swabbed with the secretion from one of our patients, but nothing resulted.

The blood serum of one patient was tested for agglutinins with each of the bacterial strains recovered from the cultures. The results were negative excepting with *Döderleins lactobacillus*.

Efforts were made on two occasions to determine the character of the gas—14.5 c.c. was aspirated into a syringe, the plunger anointed with petrolatum jelly and the gas aspirated from the base of the cysts. All tests were conducted in the syringe at 24° C., by emersion in water at that temperature. Sulphine acid 5 per cent was first drawn into the syringe and shaken for fifteen minutes with the needle submerged. There was no reduction in volume, which was interpreted as a failure to demonstrate trimethylamine, a gas claimed by Zweifel and early investigators as present. This gas has a fishy odor and occurs in the vaginas of pregnant and nonpregnant women. The acid was washed out with water and replaced with 1.7 normal sodium hydroxide and also shaken with the gas for 15 minutes. Again there was no absorption excluding carbon dioxide.

Saturated pyrogallie acid was drawn into the syringe and mixed with sodium hydroxide. The surface of the liquid in the syringe became dark and during two hours' contact, with frequent shaking there was a reduction of about 21 per cent in volume, suggesting oxygen. The remainder was tested for inflammability with negative result. If it were nitrogen the composition of the gas would seem to be practically identical with that of air. These experiments were carried out by Dr. Robert Hill of the biochemical department of the University.

In order to investigate the persistence and reaction produced by gas in the tissues, experimental subcutaneous emphysema was produced by injecting air subcutaneously in a rabbit. Five days later the rabbit was killed. Postmortem examination showed scattered patches of small gas-containing vesicles in loose areolar tissue with no gross evidence of inflammation. Sections of the tissue showed small empty vesicles with thin walls, surrounded by scattered lymphocytes and monocytes, a few multinuclear giant cells, partly lining the cysts, supports the view that tissues react to gas somewhat as to the presence of a foreign body.

Singh has stated that oxygen is absorbed slowly from the tissues and may remain under the skin for a week.

Nagashima in 1924 described four museum specimens and two fresh cadavers in the pathological institute of the University of Berlin and pointed out a condition which is present in our first case but not observed in the second. Irregularly shaped interpapillary downward extensions occur, some of which lay in the lamina propria and are apparently completely separated from the surface epithelium. In some of the down growths of epithelial cells there is a central space partly filled by desquamated squamous cells, erythrocytes and polymorphonuclear leucocytes. Elsewhere the surface epithelium contains several small empty vesicles from 0.5 to 1 mm. in diameter.

He with others believe that the cysts arise primarily in the epithelium, penetrating later into the lymph spaces where gas is formed by bacterial action. He claims to have demonstrated bacteria by special staining methods, the order being penetration of "epithelial nests," liquefaction, cavitation, and gas production.

TABLE III. POSITION OF FETUS

| | |
|--------------|----|
| Anterior | 15 |
| Posterior | 2 |
| Breech | 1 |
| Not recorded | 6 |

Fifteen were anterior positions, two were posterior, one was a breech, and six were not recorded.

TABLE IV. CLINICAL SIGNS OF INVERSION OF UTERUS

| | POSTPARTUM HEMORRHAGE | SHOCK | PROLAPSED UTERUS |
|---------|--------------------------|-------|---------------------|
| Present | 20 | 19 | 5 |
| Absent | 4 | 5 | 19 |

Twenty patients hemorrhaged and in four the blood loss was considered normal. Nineteen patients went into shock and five did not.

TABLE V. LENGTH OF THIRD STAGE

| | | |
|---------------|----|--------------|
| 0-30 minutes | 13 | 2 Fatalities |
| 30-60 minutes | 2 | 0 Fatalities |
| 1- 2 hours | 2 | 1 Fatality |
| 2 hours | 1 | 0 Fatalities |
| Unknown | 6 | 3 Fatalities |

The third stage was apparently normal in length of time in thirteen cases, prolonged in five cases, and unrecorded in six.

TABLE VI. TIME OF DIAGNOSIS (AFTER END OF THIRD STAGE)

| TIME | NUMBER | FATALITIES |
|---------------|--------|------------|
| 0-30 minutes | 10 | 2 |
| 30-60 minutes | 1 | 0 |
| 1- 2 hours | 2 | 0 |
| 2- 3 hours | 1 | 1 |
| 3- 4 hours | 1 | 0 |
| 4- 5 hours | 2 | 0 |
| 6 hours | 1 | 1 |
| Unrecorded | 3 | 2 |
| 7 days | 1 | 0 |
| 14 days | 1 | 0 |
| 6 weeks | 1 | 0 |

In ten the diagnosis was made at once and, of these, two died. In eleven cases diagnosis was delayed from one-half to six hours and four patients died. In three other cases, the condition was not recognized until seven and fourteen days, and six weeks, respectively, after delivery. All patients recovered after manual replacement.

TABLE VII. TIME OF DEATH POST PARTUM

| | |
|---------|---------------------|
| Case 1 | 6 hours, 35 minutes |
| Case 2 | 6 hours, 10 minutes |
| Case 3 | 3 hours, 34 minutes |
| Case 5 | 4 hours, 40 minutes |
| Case 9 | 3 hours, 33 minutes |
| Case 11 | 5 hours, 55 minutes |
| Average | 5 hours, 5 minutes |

PUERPERAL INVERSION OF THE UTERUS*

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(From the Providence Hospital)

THE subject of inversion of the uterus has been quite thoroughly discussed in the medical literature, yet there still seems to be a lack of unanimity of opinion as to both the cause and treatment of this serious postpartum emergency. The condition is sufficiently rare to make the experience of the average obstetrician inadequate to draw satisfactory conclusions from his own practice. For this reason we have collected a series of twenty-four cases from the records of Providence Hospital, Detroit, over a period of sixteen years. Most of these patients have been personally observed and treated in consultation. They represent an incidence of one in 2,300 deliveries.

It is a significant fact that all but three of the cases were managed by general practitioners, and the patient was not seen by the consultant until her condition became critical. In nearly all cases we were unable to get a history of aggressive management of the third stage, and further evidence of the inaccuracy of the case records is seen in the estimation of blood loss. The figures obtained from the charts probably represent only a fraction of the total hemorrhage. This is particularly apparent in the fatalities where exsanguination and shock were the cause of death.

TABLE I

| NO. OF CASES | PARITY | FATALITIES 25% |
|--------------|-----------------|------------------|
| 24 | Primigravida 16 | 2 |
| | Multigravida 8 | 4 |
| | | (All gravida ii) |

In this series, the age of the patients varied from 17 to 33. Sixteen were pregnant for the first time and eight were multiparae.

TABLE II. TYPE OF DELIVERY

| | |
|-------------------|----|
| Spontaneous | 18 |
| Low forceps | 3 |
| Breech extraction | 1 |
| Not recorded | 2 |

There were eighteen spontaneous deliveries, three were delivered by low forceps, one was a breech extraction, and two were not recorded.

*Read before the Central Association of Obstetricians and Gynecologists on Oct. 24, 1947, in Louisville, Ky.

sepsis and development of a contraction ring make replacement difficult. Here immediate replacement is advised. Second, the intermediate period, when the above conditions have supervened, and Barrett contends that conservative treatment is indicated. In the late period, when these adverse conditions are under control, replacement is done by an appropriate method.

McKelvey² is even more conservative. He treats the shock and hemorrhage and disregards the inverted uterus, treating it some weeks later by an appropriate surgical procedure. Cosgrove³ reports no deaths in his series in those cases which were promptly diagnosed and replaced. Fatalities occurred only where diagnosis and treatment were delayed. Phaneuf⁴ reports five cases treated, one by manual replacement, one by abdominal panhysterectomy and bilateral salpingo-oophorectomy, and three by the Spinelli operation. Harer and Sharkey⁵ report twenty-one cases with nine deaths in which mismanagement of the third stage was the chief etiological factor. They employ the immediate replacement of the uterus and make no mention of surgery in their management of this complication.

Das⁶ reporting from Calcutta, where inversion seems to be more common than in the United States, advises immediate replacement if possible. If this cannot be done, he recommends treatment of shock and hemorrhage, and, at a later date, the use of the Spinelli operation or the abdominal approach. Salvin⁷ observes the much greater frequency of inversion in cattle and emphasizes the point that mismanagement of the third stage may be a less important factor than we have been led to believe. In none of our series were we able to get a history of mismanagement of the placental stage, but it is a significant fact that in only three of twenty-four cases was the patient in the hands of an experienced obstetrician. Stander,⁸ in the third revision of his text, advises immediate replacement under general anesthesia, but if shock is severe, he counsels treatment of the shock and hemorrhage before manipulations are undertaken. In chronic cases he advises operation, utilizing the technic of Haultain, Huntington, or Spinelli.

In practically every report in recent years, the treatment of inverted uterus is covered by generalities. Replacement at once if possible is always advised. Treatment of shock and hemorrhage first is usually advocated, with replacement when the patient's condition has improved. Surgical treatment in the chronic stage by several methods is advocated. It is our contention that manual replacement immediately upon diagnosis is not only possible but advisable, being combined of course with vigorous antishock therapy. We feel furthermore that the surgical treatment of this condition is unnecessary in the vast majority of cases, and we point to the fact that we have not used it once in twenty-four cases, and three of these were replaced seven, fourteen, and forty-two days, respectively, after the onset of the condition.

The lack of unanimity in the literature is exemplified in a case recently reported by Reid, Turner, and Summers⁹ in which a referred patient was seen three and one-half hours after delivery. She was in collapse and was treated with glucose, plasma, and blood transfusions. Six hours after delivery, vaginal examination revealed an inverted uterus and apparently an unsuccessful attempt was made to replace the organ manually. Two hours later, an abdominal operation was done and the uterus replaced by the method of Huntington under local anesthesia. Despite continuation of active shock therapy, the patient died two days later.

Many cases of inverted uterus are seen by skillful operators who may be confronted with this condition for the first time. Of necessity, they must rely on the consensus of opinion expressed by the literature on the problem of choosing the treatment. Their failure in properly managing these difficult cases

The six fatalities all occurred within six hours. The shortest period of time between delivery and death was three hours and thirty-three minutes. This allowed plenty of time for diagnosis and active treatment if the attending obstetrician was alert to the condition of his patient.

From the etiological standpoint, these figures indicate that age of the patient, position of the fetus, and surgical intervention apparently have no influence on the development of inversion. It is significant that sixteen of the twenty-four were primiparas and that in one case, the condition recurred at the next delivery. This suggests a congenital predisposition to inversion, possibly the result of variation in the uterine musculature or its innervation. In five cases, the third stage was prolonged, and in two, a manual removal of the placenta was done. Both of these patients died.

We are forced to conclude, then, that in certain patients there is a predisposition to inversion, and if this is combined with an abnormal or mismanaged third stage, inversion may occur. Therefore, it is our practice to avoid vigorous manipulation of the uterus because it interferes with the normal mechanism of separation and predisposes to retention of placental fragments. It is now our custom to give an ergot preparation intravenously as the child is delivered. The fundus is held, but not massaged unless it relaxes. Massage is accomplished by a rotary motion with the flat of the hand, using the vertebral column as counter pressure. Pressure should not be exerted in the direction of the birth canal. The placenta usually separates in a few minutes, and, as a rule, is expressed before the repair is done. If separation is delayed and general anesthesia is being used, we complete the repair rather than attempt premature expression. We do not like to prolong the use of general anesthesia, but if some form of regional block has been used, we wait for the end of the third stage before reconstructing the perineum.

In this series the problem of diagnosing inversion was complicated by the fact that only five of the cases were accompanied by prolapse of the uterus. In nineteen, the diagnosis had to be made on the basis of shock and hemorrhage, abdominal and vaginal examination. The findings on abdominal examination are unreliable because the inverted fundus is in the normal position in the pelvis, and if the examination is careless or if the abdominal wall is thick, the characteristic dimpling of the uterine tumor is not noted. In not one of these twenty-four cases was this sign of diagnostic value. For this reason, we have made it a rule that in all cases of hemorrhage, with or without shock, a vaginal examination is made at once. The boggy mass of the inverted uterus poses no diagnostic problem if it is looked for. Only ten of our cases were diagnosed promptly, although all patients were treated for shock and hemorrhage. Shock is out of proportion to the amount of blood lost, and this alone should make us suspicious of inversion. This is due no doubt to traction and pressure on the plexus of nerves in the broad ligaments as they are dragged through the hernial opening. If treatment is delayed, the combination of loss of blood and shock may produce a condition so severe that it becomes irreversible and the patient may die despite adequate amounts of blood replacement. Of the six deaths in this series, all patients died within six hours after delivery. All six, however, were given intravenous fluids and five were transfused. These deaths were recorded, two in 1931, one each in 1932, 1935, 1940 and 1941. By present standards of shock therapy, treatment in all cases was inadequate inasmuch as 500 c.c. represented the maximum amount of blood replacement.

The trend in treatment as expressed by the more recent literature is best exemplified by Barrett,¹ who describes three periods in this condition: first, the immediate period when shock and hemorrhage are not too severe and before

the vulva. She was taken to the operating room and under anesthesia the uterus was replaced by the technic of ring forceps on the cervix and manipulation of the fundus. She made an uneventful recovery. Another patient made an apparently normal recovery from a spontaneous delivery and went home on the tenth day. On the fourteenth day, she hemorrhaged and her physician sent her back to the hospital with a diagnosis of placental polyp. Vaginal examination revealed an inverted uterus and under ether, it was replaced by use of the same technic, without a cutting operation.

In the last case of delayed diagnosis the patient hemorrhaged at the time of delivery and was treated by transfusions. She recovered but continued to bleed excessively. Six weeks later she was referred to one of us (R. W. A.) and a diagnosis of chronic inversion was made. Operative interference was considered, but an attempt was made to replace the uterus by taxis. This was successful and she made an uneventful recovery.

Comment

Inversion of the uterus is a serious postpartum complication with a high primary mortality. It is probably more common than the literature indicates and undoubtedly many deaths ascribed to postpartum shock and hemorrhage are due to the concealed variety of inversion. To substantiate this statement, we have the record of a recent case not included in this series, in which death occurred several hours after delivery. Autopsy revealed an inverted uterus. By present-day standards, her treatment for shock and hemorrhage was adequate.

All cases of abnormal postpartum bleeding should be investigated immediately to rule out inversion. Manual replacement should be done at once and not delayed. Transfusions and other intravenous therapy must be carried on at the same time.

Shock is due in part at least to stretching and pinching of the nerve plexus in the broad ligaments, and an integral part of the treatment is directed toward relieving this condition by immediate replacement. Therefore, there is no place in the management of acute puerperal inversion of the uterus for delay in replacement of the herniated organ. Replacement can be made early with little difficulty, by the average operator, without anesthesia in most instances, and without increasing shock.

We have had no experience in the treatment of inversion of the uterus by surgery. Since we have treated patients as late as seven weeks postpartum without either vaginal or abdominal operations, we contend that replacement by taxis is not only possible but preferable in practically every instance.

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rests on the shoulders of us whose greater experience should guide them in their procedures. Immediate diagnosis of the cause of postpartum hemorrhage and prompt active treatment will save many of these women.

We have attempted to formulate a definite policy of diagnosis and treatment from a study of these twenty-four cases. They cover a period of time during part of which blood banks were unknown and donors had to be found, typed, and cross-matched. Blood was therefore obtained late and in inadequate amounts. Plasma to tide us over while waiting for blood was not available. Four of the patients in first five in this series died, and the last six have all survived. None of the six fatalities received over 500 c.c. of blood, and one was not transfused at all. This indicates that better results in later years are due to improvement in the availability of treatment for shock and hemorrhage. Two of eleven patients diagnosed within an hour died, and three of thirteen died where the diagnosis was delayed. This does not invalidate our plea for early diagnosis, because when shock and hemorrhage are most severe, consultation is called early and diagnosis is more prompt. When the patient's condition is not so alarming, the condition is apt to be overlooked. For example, in our series, in cases diagnosed one, two, and six weeks after delivery, there was no evidence of shock.

All the fatalities occurred within the immediate period referred to by Barrett as the time for active intervention. During this period hemorrhage is continuing and shock is increasing. Blood and supportive measures are not usually enough to combat the condition. The stretching and pinching of the nerve plexus in the broad ligaments and ovaries is sufficient to negate the value of our therapeutic measures. Since replacement at this time is so simple that it can be done in a minute or two and usually without anesthesia, we have adopted the policy of immediate replacement.

To illustrate this point, a 22-year-old para 0 gravida i was delivered normally at 4:10 P.M. with a reported blood loss of 200-300 c.c. She was very restless and at 5:30 was given 1/32 gr. of dilaudid. After this she hemorrhaged profusely and was given ergot and 1,000 c.c. of glucose in saline. Her blood pressure dropped to 60/40 and at 6:50 she was given 500 c.c. of blood. Blood and plasma were continued and oxygen administered. The patient's pulse became imperceptible and respiration stopped. She was being given artificial respiration by means of the gas machine when seen by one of us (H. H.) at 8:30 P.M. At this time blood and plasma were being given into both arms. Examination showed an inverted uterus and it was immediately and easily replaced, and almost instantly her pulse improved and spontaneous respiration started. She made a febrile but complete recovery and became pregnant again two years later.

The replacement of the acute puerperal uterus is simple and usually does not require a high degree of skill. Three of these cases were discovered and replaced by the attending physician or the resident. Ring forceps clamped on the edge of the cervical rim accompanied by traction with counter pressure on the inverted fundus will readily correct the inversion. Packing may be resorted to if necessary to keep the uterus in place, but this is not usually needed. In none of the above cases was there any difficulty in this maneuver, whether it was done by the consultant, the attending physician, or the resident.

A different problem exists in the type of inversion that escapes diagnosis at the time of delivery and is discovered at a later date. Three of our cases fall in this category. One patient who had hemorrhaged moderately, continued to bleed despite ergot, and was unable to void. She was sent to the bathroom on the seventh day and while straining, the entire inverted uterus came out of

uncomplicated labor. According to the charts there was no complication in the first stage. The condition occurs rarely in the practice of any physician. In these nine cases it never occurred more than once in the practice of any one individual. Five of the cases occurred in the practice of individuals with limited obstetric preparation; two were staff cases and were delivered by residents or interns. Four of the nine were recognized immediately or very early and had no morbidity. It was interesting that in this group of four without morbidity one of the cases was observed following manual removal of the placenta at the time of cesarean section. It was immediately corrected. It is also interesting to observe that one of these cases was immediately replaced presumably and packed and the patient returned to her bed; she continued to bleed and was brought back for re-examination. The consultant took her to the operating room and did a laparotomy and found the first operator had perforated the uterus, so hysterectomy was done. She had no postpartum or postoperative morbidity. In the cases with postpartum morbidity it was not in excess of five days. Discovery of the condition was immediate in two cases and the cases were treated by replacement, transfusion, and treatment for shock. One of the cases with morbidity was not discovered until the patient had been in her room for two or three hours and continued to bleed. She was brought back and examined. The consultant did a laparotomy, replaced the inversion by abdominal route and sutured the uterus to the abdominal wall, bringing the suture out through the wound and tying it over a glass rod. I mention this as an unusual method of treatment. One of the cases of morbidity was discharged on the tenth day but at home continued to bleed. After six weeks she was brought back and operated abdominally. This was a chronic inversion. She was treated by fixation of the uterus and sterilization. The woman who died is one from which we should draw considerable conclusions. It occurred in a small institution where there are no interns or residents. There are facilities for blood transfusion. The attendant had never seen inversion before. As soon as it was discovered that she was bleeding he called for help and it happened that I was the one he called. I was, however, in attendance on another patient in another hospital and he finally obtained the help of a general surgeon who came in and took her to the operating room; the inverted uterus was amputated and the patient put to bed. While efforts were still being made for transfusion she died. Because of the occasional experience that puerperal inversion of the uterus occurs and is not discovered until the patient has gone back to her room, many of us have felt that routine examination of the cervix with a retractor and ring forceps is a worth-while procedure to prevent the occasional unrecognized puerperal inversion.

DR. RUDOLPH W. HOLMES, Charlottesville, Va.—Drs. Henderson and Alles must be congratulated on their unique experience with 22 cases of puerperal inversion seen in consultation. In the last century inversion was estimated to occur once in 100,000 labors; by Hirst once in 140,000; in the Rotunda once in 190,000, and none in Carl Brann's services in 250,000 labors. That inversion has been reported more frequently these late years is indisputable; that the anomaly is more frequent these days, due to a devitalization of the uteri of modern women, is manifestly a spurious implication. We must believe that in times long past few women were examined post partum, so the inversion was not discovered; in our modern world the routine post partum, and follow-up examinations, gives us an increased incidence due to discovery alone.

It was a vicious preachment that inversion was due to mismanagement on the part of the attendant, for I am firmly convinced that it is more the result of malign forces within the uterine body (is spontaneous in origin) rather than brusque Dublin or Crede maneuvers, or other mechanical forces. In a collaborated text book some forty years ago, under inversion, it was stated that inept conduct of the third stage was the responsible cause: under treatment of the third stage the recommended procedures were so crude most women who were so treated would have had inversions if it were not for inherent abnormalities in the uterus itself.

So far as I know no one has added anything to the mechanics of inversion since Barnes and Radford expounded their theories for the mechanics. The production of an inversion by eversion of the uterine wall (Taylor's mechanism) is probably of pure historic interest,

Discussion

CURTIS J. LUND, M.D., New Orleans, La.—Two aspects of this uncommon complication of pregnancy are of particular interest. The first is the wide variation noted in the incidence which ranges, according to reports, from 1:740 to 1:16,000 deliveries. At Charity Hospital seven inversions with one death have been observed during the past forty years. The incidence has declined steadily, and at the present time only two cases have been observed in over 90,000 deliveries.

The second point of interest centers about the controversy between (1) those who believe that immediate replacement is an essential part of therapy, and (2) those who postpone replacement for weeks. Divergent as these ideas may be, they have one common denominator which is the treatment of shock.

The results presented today, the results of other investigators as well as our own, indicate that most deaths occur within a few hours and are accompanied by profound shock. Of the few late deaths reported, most are associated with premature attempts at replacement. Deaths from infection have been conspicuously infrequent. Such findings make it obvious that therapy must be focused on shock. With what type of shock are we dealing?

There is little doubt that the shock of the inversion is often out of proportion to the blood lost. The authors attribute this to stretching and pinching of the nerves. This is likely correct and would fit into the classification of primary or neurogenic shock, as described by Blalock, Moon, and others. Such shock is characterized by vasodilatation; it is of short duration and is unaccompanied by hemoconcentration. Uncomplicated primary shock is not especially serious until there is superimposed hemorrhage or secondary traumatic shock. Many of you have seen patients recover partially from the initial inversion only to relapse suddenly into profound and frequently fatal secondary shock. However, in practice the accident is often associated with postpartum hemorrhage so that the primary shock is obscured and no recovery period is noted.

It is the secondary or traumatic shock which kills unless quickly and adequately treated. We cannot overemphasize that adequate treatment usually requires enormous amounts of blood and plasma as it is not unusual to find hemoglobin levels of 4 or 5 Gm. after the initial shock and its hemoconcentration has been overcome.

It would appear that the real value of immediate replacement lies in the treatment of primary neurogenic shock. This stage is relatively short so that the effectiveness of reposition becomes inversely proportional to the duration of the inversion. For this reason we believe that immediate replacement should be limited to those patients (1) who can be treated within two or three hours of the inversion, (2) upon whom replacement is readily performed without deep anesthesia or extensive manipulation, and (3) who are not exsanguinated or in serious secondary shock. It must be clearly understood that successful reposition in no way eliminates the need for vigorous therapy of shock.

Those who advocate conservative therapy have clearly shown that death can be virtually eliminated but at the cost of prolonged and vigorous therapy. Successful immediate replacement can be followed by a rather short and uneventful convalescence in carefully chosen patients, but it must not become a factor contributing to the mortality of the disease.

DR. PALMER E. SUTTON, Royal Oak, Mich.—At the risk of some repetition I wish to make a few observations. Puerperal inversion of the uterus has occurred at Woman's Hospital in Detroit eight times since 1929; eight times in 47,576 deliveries, an incidence of 0.0168, without mortality. I would like to contrast this incidence and this result with the incidence in one other institution where puerperal inversion has occurred only once in a series of 1,679 deliveries with one death. The combined incidence is 9 cases in 49,000 deliveries.

As Dr. Henderson and Dr. Lund have pointed out, gravity, parity and other such factors do not seem to enter into the problem. In all nine instances the cases were those of

Dr. Fischmann described the three varieties of inversion. The first type is not usually discovered because in most instances it goes back spontaneously. In our series, nineteen were complete inversions but not exteriorized. Dr. Fischmann also asked about the placenta. In one of our cases the uterus came out with the placenta in place. We decided the best thing to do was to replace the uterus with the placenta intact, which we did, and then very carefully watched the third stage. It was not long before the placenta came out. He advocated the use of adrenalin. We have not had success with it.

So far as recurrence is concerned, we had three inversions during the last year which had occurred elsewhere, and the women came to us in a subsequent pregnancy, one of them being pregnant for the second time following inversion. We have delivered all three of them without difficulty and without recurrence of the inversion. We were looking for a recurrence and managed the third stage with that in mind.

which is comparable to the process of the dunging of a horse. The true mechanism presages a softened, relaxed area at or near the fundus: the rim of the depression contracts which forces the introcedent wall downwards: as the depressed wall descends, in turn, lower areas of the uterine wall contract and force it down lower and lower until the inversion is completed. This mechanism is the key-note in the method of replacement. That a grossly relaxed, atonic uterus may be forced out by abdominal pressure may be unquestioned.

The fundamentals of treatment comprise these steps: (1) Immediate reposition on discovery, with or without anesthesia: remove the placenta (if still adherent) only after first attempts are futile: (2) The replacement must progress in the inverse order to that which occurred in the production—i.e., that which inverted last must be returned first, until the fundus has returned to its normal situs. By this method only *two* thicknesses of the introcedent wall pass through the cervix: the attempt will usually fail if the fundus is first forced upward as thereby *four* thicknesses must necessarily be crowded through the cervical canal. (3) After reposition, whether there be hemorrhage or not, the uterus and vagina must be firmly tamponed. A mere vaginal tampon is an absurdity. (4) Shock and hemorrhage must be combated.

In line with what has been stated the placental implantation is commonly found near or at the fundus.

DR. E. W. FISCHMANN, Chicago.—In inversion we usually describe three varieties. In the first, there is a depression or cup-shaped depression of the fundus. In the second, the fundus of the uterus comes through the cervix but does not come down into the vagina. The third variety is complete inversion. I think it is important to make an abdominal palpation on all cases immediately post partum. I have seen several cases in consultation where the condition was not recognized for several days post partum because there was no such abdominal examination made.

I want to ask the essayist how he treats the cases in regard to the placenta. Complete inversion of the uterus occurs in some cases where the placenta is still attached to the fundus or the interior of the uterus. We have had success by using small doses of adrenalin injected into the uterine musculature prior to any attempt at immediate reduction.

The essayist mentioned one case in which subsequent pregnancy occurred after inversion. We have had three cases in which the patient has had a subsequent pregnancy, and in one case two subsequent pregnancies, so all cases of inversion of the uterus are not necessarily followed by morbidity or conditions which may prevent subsequent pregnancy. Furthermore, inversion of the uterus does not recur in subsequent pregnancies. I have scanned the literature rather carefully and have found no such cases reported.

DR. HENDERSON (closing).—The experience of Dr. Lund and Dr. Sutton is similar to ours. I also work in two hospitals. In Harper Hospital we found several cases over a period of years while in the Providence Hospital, where a large part of the work is done by local practitioners, the incidence has been appalling. As the hospital staff has changed to younger and better trained men, the incidence of inversion of the uterus is greatly decreased.

As Dr. Lund has said, there are two types of shock in this condition; one is the result of hemorrhage and the other the result of trauma. We can increase traumatic shock by manipulation, but those same manipulations can be done in such a way as not to increase the shock. That brings up the point of the technic of replacing the uterus. Dr. Holmes has emphasized that the uterus must be replaced in the same order in which inversion occurred, and that if you push the fundus back, you have four layers of uterine wall to go through the cervix. If you remember that, and take hold of the cervix with ring forceps, and push the fundus with a little traction on the cervix, you will find it will go back in the same way it comes out. That is why we have had success in our treatment.

Listening to Dr. Sutton's discussion emphasizes our reasons for being insistent on the more conservative management of this condition.

case was a near fatality upon numerous occasions. After twelve months, she is still in a respirator and has quadriplegia and diaphragmatic paralysis. Two more patients have severe residual extremity paralysis. These results contrast sharply with the recoveries experienced by early pregnancy patients, in whom only two out of nineteen suffered permanent damage. Although the series is small, the mortality rate of 50 per cent in the last trimester greatly exceeds that of 6 per cent for the entire Colorado epidemic and 8 per cent for the eighty-eight nonpregnant women in the age group under consideration. The difference between the course of poliomyelitis contracted early in pregnancy and that occurring during the last trimester is striking.

Support for the validity of this observation was obtained by a re-examination of previous reports of coincident poliomyelitis infection and pregnancy. We were able to collect from many sources one hundred seventy additional cases in whom the trimester of pregnancy and the course of the disease were known.^{2, 3, 5-12} Weaver and Steiner⁵ in 1944 provided in their article an extensive tabulation of cases bearing upon the subject. Grelland⁶ in 1947 summarized similar data for fifty-eight cases in the Scandinavian literature. None of these series was large enough to indicate the extreme difference in prognosis for early and late pregnancy. However, when examined collectively, it is apparent that our data are significant. Of one hundred ten first and second trimester patients, there were eight deaths or a 7 per cent mortality rate. On the other hand, among eighty-five last trimester cases, twenty-three patients or 27 per cent died from bulbar poliomyelitis.

Some writers have said that hormone changes influence susceptibility to the virus of poliomyelitis.¹³⁻¹⁷ Animal experiments have suggested that increased estrogen titer is protective to a host attack by the disease.^{13, 14} Our clinical evidence refutes such a hypothesis for, during late pregnancy when women are most abundantly supplied with estrogen, their resistance to the virus is poorest.

Anderson,¹⁴ experimenting upon mice infected with a murine type of poliomyelitis virus, was able to demonstrate the protective nature of both estrogen and progesterone. We know that progesterone is present in its largest amounts during the last months of pregnancy. The body stores of progesterone and estrogen do not protect the last trimester pregnant woman from the virus.

Chorionic gonadotropic hormone has been said to be protective against poliomyelitis.^{5, 16, 17} There is some experimental basis for such thought.^{5, 17} If this were true, it should be particularly so during early pregnancy when its titer is highest. Actually, the incidence of poliomyelitis at this time is greater than in the normal population. Further, we know that this hormone remains in the blood until the end of pregnancy, even if in reduced amounts. It is difficult, then, to reconcile its value when late pregnancy cases with measurable amounts of the gonadotropin fare so poorly.

Notwithstanding, it is obvious that the manner in which poliomyelitis afflicts pregnant women differs greatly from its effect upon other segments of the population. According to our observations, patients who contract poliomyelitis before the seventh month of pregnancy are likely to recover with little or no paralysis. The recovery seems to take place in spite of an increased susceptibility. Estrogen and progesterone might then be considered protective in early pregnancy. What happens during the last trimester? The progressive rise in estrogen and progesterone is conveniently coincident with the sudden appearance of serious disease in the last months. These two hormones may have been protective during early pregnancy but in the last months the increased amounts of estrogen and progesterone would have to be virucidal to such a marked degree that a Herxheimer-like reaction is produced. Extensive inflammation, edema, and necrosis of anterior horn and bulbar nuclei cells may be

ACUTE ANTERIOR POLIOMYELITIS IN PREGNANCY*

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DURING the summer and fall of 1946, there were nine hundred new cases of poliomyelitis reported in Colorado. Of these, one hundred thirteen were among women between the ages of seventeen and forty. Of the twenty-five who were pregnant, seventeen were treated by the staff of the University Hospital.

It has been estimated that 11.7 per cent of Colorado's women between seventeen and forty were pregnant on any given day during the epidemic. Twenty-two per cent or twice as many of the poliomyelitis victims in the same age group were pregnant. Our experience corresponds with that of others,¹⁻⁴ who have suggested that pregnant women have a predilection for poliomyelitis. Our incidence of poliomyelitis during pregnancy has been subjected to statistical analysis and has been demonstrated to be significant (the standard error between the two groups is 3.5). This analysis also indicated that a pregnant woman in Colorado during this period had one chance in a thousand for contracting the disease.† What are the answers? Why does it happen? Let us review the experience gained from our epidemic.

Epidemiologic Aspects

Of the twenty-five acute poliomyelitis cases accompanied by pregnancy, eight appeared in the first trimester, eleven in the second, and six in the third. Each of the nine months was represented.

In another study, Aycock¹ summarized two hundred thirty-six cases with pregnancy and poliomyelitis and found the distribution of cases as follows: fifty-three in the first trimester, ninety in the second, and ninety-one in the last.

Although the pregnant woman in Colorado during the epidemic seemed to be twice as susceptible to the virus as her nonpregnant sister, there were some compensations if she contracted the disease during the first two trimesters of pregnancy. Of nineteen patients in the first and second trimesters, there were no fatalities, and only two of the nineteen have significant residual paralysis (see Table I). On the other hand, of eighty-eight nonpregnant, seventeen to forty-year-old women who had poliomyelitis during the same epidemic, 66 per cent had the paralytic form of the disease and seven of these patients died of bulbar poliomyelitis. Perhaps there is something about the first six months of pregnancy that makes the disease more easily contracted and yet a milder one.

The six patients who fell ill during the last three months of pregnancy had a very different and tragic course. During the last trimester, the prognosis is terrifying. There were three deaths from bulbar paralysis. A fourth bulbar

*Read before the Central Association of Obstetricians and Gynecologists on Oct. 24, 1947, in Louisville, Ky.

†The calculations were made by Dr. Lloyd Floris, Professor of Public Health, University of Colorado School of Medicine.

rate while eighty-five last trimester cases had a 27 per cent mortality rate. This difference in severity of the disease during late pregnancy is striking. It is suggested that the increased permeability of the upper respiratory and digestive tracts to the poliomyelitis virus during pregnancy and the fatigue of pregnancy are important in accounting for the increased incidence of the disease. Nineteen of our patients, who fell ill during the first six months of their pregnancy, had no mortality and suffered none of the severe paralytic end results of the disease. However, our six last trimester of pregnancy cases did very poorly. Three of them were fatalities and three developed permanent severe paralysis. Perhaps, estrogen and progesterone are protective to the pregnant poliomyelitis victim early in pregnancy. In the last trimester of pregnancy, these hormones are not protective. However, they may be virucidal to such a profound degree that a Herxheimer-like reaction is created within the host, causing irreversible tissue damage.

Table I summarizes each of our twenty-five cases. It will be noted that these patients are arranged according to their week of pregnancy. The two right-hand columns on the table show that the more advanced the pregnancy, the more grave the prognosis for the poliomyelitis.

TABLE I. SUMMARY CHART OF 25 ACUTE POLIOMYELITIS AND PREGNANCY CASES

| PATIENT | AGE | PARITY | DELIVERY | INFANT | WEEKS OF PREGNANCY AT ONSET | POLIOMYELITIS RESIDUAL |
|---------|-----|--------|------------------------------|---|-----------------------------------|------------------------------|
| M. H. | 29 | 2 | Spontaneous | Normal M. | 4 | None |
| C. A. | 17 | 0 | Spontaneous | Normal F. | 4 | None |
| R. W. | 25 | 2 | Spontaneous | Normal F. | 6 | None |
| J. P. | 24 | 0 | Spon. abortion, 7 weeks | ? | 6 | Mild |
| N. L. | 25 | 3 | Spontaneous | Normal M. | 6 | Mild |
| L. M. | 24 | 1 | Spontaneous | Normal F. | 10 | None |
| E. T. | 39 | 6 | Spontaneous, twins | Normal M. & F. | 11 | None |
| B. F. | 32 | 1 | Spontaneous | Normal M. | 12 | None |
| R. M. | 25 | 1 | Spontaneous | Normal F. | 13 | Moderate |
| H. A. | 33 | 2 | Spontaneous | Normal M. | 14 | Minimal bulbar |
| E. J. | 27 | 1 | Spontaneous | Normal M. | 15 | None |
| P. Y. | 19 | 0 | Spon. abortion, 20 weeks | Male | 19 | None |
| C. S. | 22 | 2 | Spontaneous | Normal M. | 19 | Minimal Bulbar-spinal |
| D. H. | 22 | 0 | Spontaneous | Male; died, 28 hr., pneumonia | 19 | None |
| I. M. | 19 | 1 | Low forceps | Normal F. | 21 | Moderate |
| B. B. | 22 | 0 | Assisted breech | Normal F. | 22 | Mild |
| M. M. | 29 | 1 | Spontaneous | Normal M. | 23 | Mild |
| L. G. | 27 | 0 | Spontaneous | Normal M. | 26 | None |
| L. J. | 24 | 0 | Spontaneous | Normal F. | 28 | None |
| B. S. | 17 | 0 | Low forceps | Normal M. | 29 | Severe |
| J. W. | 19 | 0 | Spontaneous | Normal F. | 31 | Fatal bulbar |
| L. S. | 23 | 2 | Postmortem section | Normal F. | 32 | Fatal bulbar |
| F. T. | 28 | 3 | Spontaneous | Normal M. | 36 | Severe |
| F. C. | 31 | 5 | Postmortem section, twins | M. & M. 1 stillborn 1 died, 18 days, pneumonia | 37 | Fatal bulbar |
| A. H. | 33 | 1 | Midforceps | Normal F. | 39 | Very severe Bulbar-spinal |

precipitated. This sudden and massive destruction of the neurotropic virus and the accompanying profound tissue response may account for the severity of the disease in late pregnancy. Such an explanation will reconcile animal experiments and clinical observations.

The changes in hormone metabolism fail to explain the increased incidence of poliomyelitis among pregnant women. Two factors seem important to us. One is that pregnancy produces a congestion and increased permeability of the upper respiratory and upper digestive tracts. Such a condition may provide a more advantageous port of entry for the virus. A second factor that may play a role is chronic fatigue. In nonpregnant individuals, this has been observed to be a predisposing factor to poliomyelitis.¹⁸⁻²¹ Pregnancy in its last half means a state of chronic fatigue for most women. The favorable portal of entry and the fatigue element appear to be factors that increase the pregnant woman's susceptibility to the disease.

Obstetric Aspects

Our obstetric experience during the epidemic was interesting. The woman near term is a special problem. As we have shown, the patient usually has a severe form of the disease. Although our results are very poor for the mothers in the last trimester, one cannot see how interruption of the pregnancy will improve the prognosis. In one case, there was slight involvement until after delivery, at which time, the condition became much worse. During the acute infectious phase of bulbar poliomyelitis, a woman in her last trimester of pregnancy is a grave risk for any operative procedure.

We have delivered or had reported to us the obstetric end results of all of the twenty-five cases. Two of the twenty-five aborted early and at the time of their acute infection. There were no cases of poliomyelitis in the newborn, or congenital deformities. There were two sets of twins. Twenty-four viable infants have been delivered, thirteen male and eleven female. As has been adequately demonstrated in the past,^{22, 23} the degree of maternal spinal paralysis had no serious effect upon the labor. The uterine contractions proceeded in labor at term just as in a nonparalyzed patient. The mother's voluntary efforts at expulsion of the fetus were ineffectual in some cases due to paralysis. In this type, a low forceps operation was used as a substitute. We noticed three lower extremity paralysis cases were unable to walk until after delivery. The pregnancy had upset the skeletal balance and prevented re-education of muscle groups. We performed postmortem cesarean sections on two women who died of bulbar poliomyelitis, one at the thirty-second week and one at the thirty-seventh week of pregnancy. The first had twins, one of which was born dead, the other lived but died of pneumonia eighteen days later. A third baby, from the second mother, survived and is normal. A poliomyelitis infection during the last weeks of a pregnancy carries as grave a maternal prognosis as can befall a patient.

Summary

During Colorado's 1946 poliomyelitis epidemic, twenty-five cases of pregnancy with acute poliomyelitis were observed. The combination of pregnancy and poliomyelitis occurred twice as frequently as was statistically anticipated. The twenty-five cases were followed through delivery. There were no cases of congenital disease in the newborn. Poliomyelitis had no serious effect upon the labors of the victims. A study of our material and a study of one hundred and seventy similar cases reported by others showed that during the first six months of pregnancy, one hundred ten patients had a 7 per cent mortality

Conclusions

1. During the 1946 poliomyelitis epidemic in Colorado, the pregnant woman was twice as vulnerable to the virus disease as the nonpregnant woman of the same age group.

2. This does not mean that pregnancy should be avoided during an epidemic. The pregnant woman's chance of contracting poliomyelitis was one in one thousand. The nonpregnant woman of the same age group was exposed to an incidence of one in two thousand.

3. Women in all months of pregnancy were equally susceptible to poliomyelitis in our series.

4. During the first two trimesters, the prognosis for recovery is excellent.

5. Poliomyelitis acquired during the last trimester carries a serious prognosis for life of the mother or for escape of severe permanent paralysis.

6. Hyperemia and congestion of the upper respiratory and upper digestive tracts and fatigue of pregnancy are offered as possible explanations for the increased incidence. However, there are probably other factors at work which are more important but unrecognized.

7. Estrogen and progesterone may be protective to a poliomyelitis victim early in pregnancy. This is not true in the last trimester.

8. The virus does not pass the placental barrier. All children born of mothers infected during this epidemic have been free from congenital disease.

9. Management of pregnancy accompanied by acute poliomyelitis in the last trimester of pregnancy is a challenging problem. The policy to follow in any given case is a difficult decision. In the acutely ill patients, cesarean section seems unreasonable.

10. Poliomyelitis had no ill effects upon the progress of labor except that it necessitated an occasional forceps operation.

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Figs. 1, 2, and 3 summarize the paralytic and mortality rates observed as part of the study.

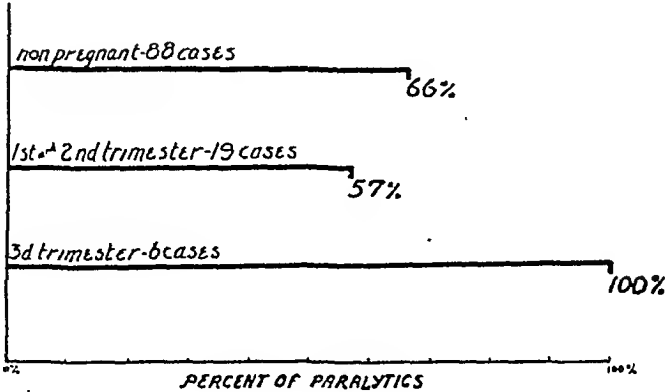


Fig. 1.

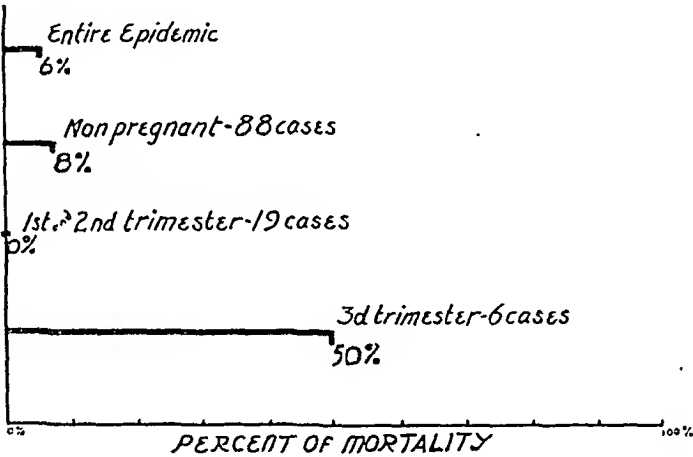


Fig. 2.

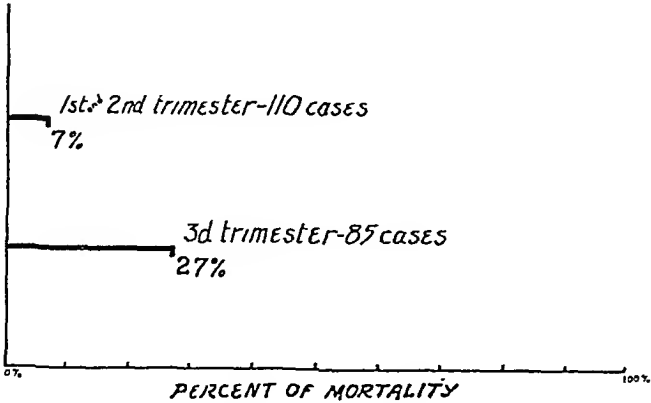


Fig. 3.

Fig. 1.—Poliomyelitis, paralytic rate, Colorado, 1946.
Fig. 2.—Poliomyelitis epidemic. Mortality rate for Colorado, 1946.
Fig. 3.—Poliomyelitis in pregnancy, mortality rate for 195 cases.

most convincing that acute poliomyelitis assumes a more serious aspect when it is associated with pregnancy.

We have admitted six gravid women to Evanston Hospital in the last two years with acute anterior poliomyelitis. Three, who were in their second month of pregnancy, recovered completely. Of these, two aborted within a week of admission. The third delivered a normal male infant at term.

Of the other three, two were in their last six weeks of gestation. One of these has a residual paralysis of the left arm, but delivered a normal female infant without difficulty. The second entered the hospital with respiratory embarrassment and died six hours later. Fetal heart tones were absent on admission and the postmortem examination revealed no evidence of poliomyelitis in the fetus. It would appear that the disease is not transmitted from the mother to the fetus.

The sixth patient developed paralysis of her legs twenty-four hours post partum. She was in the respirator for four weeks and was left with a residual quadriplegia.

One of this group had been a nurse on the contagious floor the previous year (1946) when the epidemic of poliomyelitis had been quite severe. She remained in good health, but this year, when she was no longer working in the hospital, she contracted the disease when two months pregnant. Certainly one may suspect that pregnancy increased her susceptibility to poliomyelitis.

Three of the six patients contracted poliomyelitis in the first trimester of pregnancy and recovered, although two of the three aborted.

The group who developed poliomyelitis in the last trimester of pregnancy had a much more severe form of the disease—one died, the other two have residual paralysis.

These findings are in agreement with the conclusions of Drs. Taylor and Simmons' excellent essay.

DR. LEON McGOOGAN, Omaha, Neb.—I became interested in this in 1932, at which time I saw three cases. My total experience since then has been seventeen cases of pregnancy complicated by acute anterior poliomyelitis, ten of which were seen in the Nebraska epidemic of 1946. Of this group of ten cases, one case appeared in the first trimester, six in the second, and three occurred in the third trimester, again showing a general distribution throughout the three trimesters of pregnancy. One of the patients was a primipara; the rest were multiparas.

So far as the obstetric experience is concerned, one patient miscarried, one delivered prematurely at 34 weeks; the baby was normal and survived. One died at five and a half months because of bulbar paralysis. One patient died seven and a half months pregnant, undelivered; postmortem cesarean section was performed but the baby died. The rest of the patients delivered without difficulties and without evidence of poliomyelitis appearing in the child.

As to the reason why these women are more susceptible, may I ask Dr. Taylor a question? We know that metabolism is increased during pregnancy. Is there an increased percentage of growth hormone present in pregnancy? Is it possible that the combination of increased metabolism and increased growth hormone might be an explanation as to why a pregnant woman is more susceptible to the disease?

I had in my series two postmortem cesarean sections. Both women were at the period of viability. Both had been in a respirator for from twenty-eight hours to five days. During that time they were subjected to toxemia from the pathology of the disease. Should we, for the sake of the baby, wait until the patient is moribund and then do a cesarean section, or should we do a cesarean section before the patient is placed in the respirator? By that time the prognosis is bad for the mother anyway. Could this be done under local anesthesia without any effect on the progress of the disease and with some hope of saving one of the two members?

DR. CHARLES NEWBERGER, Chicago.—I want to make the following case report. The patient, a 22-year-old primipara, was cared for prenatally in the outpatient department of Mt. Sinai Hospital. She was admitted to the hospital in September, 1938, in labor at term,

Discussion

DR. C. P. HODGKINSON, Detroit, Mich.—Acute anterior poliomyelitis as a complication of pregnancy is a relatively new obstetric problem. Subsequent to Schell's report in 1906, a number of papers have been published, the majority of which have been case reports, or collective reviews. Crystallization of thought has been hampered by lack of experience. The paper by Drs. Taylor and Simmons helps fill the gap in clinical knowledge by substantiating in some instances and discrediting in others impressions formulated from piecing together case reports. Their findings are based upon experience in an unusually severe epidemic of acute anterior poliomyelitis in a relatively confined area over a short period of time. No other report approaches this either in concentration of observation or in the number of cases reported. Such circumstances give the obstetrician a more complete and clear-cut picture of what can be expected when a patient develops acute anterior poliomyelitis. The increasing importance of this problem is emphasized by epidemiologic statistics, which show that there has been a gradually but definitely increased incidence of poliomyelitis among older age groups over the last fifty years. Dr. Taylor does not mention the percentage of adults affected in the Colorado epidemic of 1946, but apparently it was high, as 113 women between the ages of 17 and 40 were reported.

It early became apparent that four pertinent questions arose in the minds of obstetricians when their patients became infected with the virus of poliomyelitis. The consistent experience of all demonstrated that the maternal infection did not affect the baby. Moreover, the progress of the pregnancy or delivery was not materially influenced. The third question, whether the pregnancy influenced the usual course of the disease, is of special importance. Sabin, in a recent paper on poliomyelitis, stated, "One of the most important and difficult jobs in science is to ask the right question of nature." The mild course of the disease in the first two trimesters and the unusually severe course in the last trimester are difficult to correlate. Is this due to a break in immunity or to an exaggeration of the disease by the altered physiologic state of the last trimester of pregnancy? Immunologic studies are confusing, in that they have shown the sera of pregnant women to be more resistant to the poliomyelitis virus, and clinical studies are not consistent with the thought that the altered endocrine status decreases susceptibility. As pointed out by Drs. Taylor and Simmons, when estrogen and progesterin blood levels are the highest, the disease is most severe. Moreover, it appears that chorionic gonadotropin is not protective. Is the increased intracellular fluid, more characteristic of the last three months of pregnancy, a factor in contributing to the more extensive and rapid death of the anterior horn cells? The additional localized edema incited by the presence of the virus in the spinal cord may aggravate greatly the severity of the disease. Drs. Taylor and Simmons suggest a Herxheimer-like reaction to explain this increased virulence. The last major point is the apparent increased frequency during pregnancy. Here, again, the picture is clouded by many unexplained variables. Epidemiologists are unable to explain adequately the cause for epidemics. The mode of transmission of the virus, the seasonal variation of the disease, and the problems of immunity are poorly understood. Estimation of the actual incidence of the infection is pure guesswork because of the high ratio of abortive to frank cases. Pregnancy further complicates the problem and one wonders if the increase in frequency is not more apparent than real. Are there actually more pregnant women infected or does the state of pregnancy convert abortive to frank cases when the immunity barriers are violated? Drs. Taylor and Simmons mention chronic fatigue and congestion of the upper respiratory and gastrointestinal tracts as possible important factors. Until further studies clarify these points, they must remain in the field of speculation.

DR. WILLIAM J. BLACKWELL, Evanston, Ill.—Anterior poliomyelitis is no longer the exclusive concern of the pediatrician and the orthopedist. In the last few years, an increasing percentage of the adult population has been affected, until the disease has now forced itself to the attention of the obstetrician.

The occurrence of poliomyelitis in pregnancy is so infrequent that the increased dangers may not be recognized. The very fine presentation of Drs. Taylor and Simmons' study is

PROLAPSE OF THE VAGINA FOLLOWING ABDOMINAL HYSTERECTOMY*

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VAGINAL prolapse following hysterectomy is relatively rare in proportion to frequency of that operation. Although the condition is not a common occurrence, it is seen frequently enough to interest gynecologists in its prevention and cure. It has been very rarely observed following hysterectomy operations which have been performed in more recent years, and especially by surgeons who pay particular attention to pelvic surgery. There is still some difference of opinion as to the type of hysterectomy, total or subtotal, which is most likely to be followed by prolapse of the vagina. It has occurred following both types of hysterectomy, and it has been believed that removal of the cervix with severance of its supporting ligaments predisposes to prolapse of the vaginal vault. However, it is probable that factors other than the removal of the cervix are distinctly involved in this condition.

Material

The material for this study consisted of 16 cases of prolapse of the vagina, all following subtotal abdominal hysterectomy. Patients with enterocele of the posterior cul-de-sac alone following vaginal hysterectomy are not included in this group, only cases of prolapse of the vaginal vault. These cases were observed in private and hospital practice over a period of seventeen years. During this period, no such cases were observed following either total abdominal or vaginal hysterectomy. A similar, and more extensive observation, was made by McKinnon and Counseller.¹ In 24 cases of postoperative vaginal herniation, they found that 23 followed the incomplete operation and only one followed total hysterectomy.

In none of the cases reviewed in this report was the hysterectomy performed by a gynecological surgeon, or one especially interested in pelvic surgery.

Indications for removal of the uterus were not definitely obtained in every case. However, in six cases, the operation was done for myomas, and in one case, a subtotal hysterectomy was performed for carcinoma of the uterine fundus. In three cases, the hysterectomy operation was performed primarily for correction of uterine prolapse. The complaint of all of the patients when seen with vaginal prolapse, was a mass protruding from the vagina, which was more or less incapacitating. Also, dysuria and incontinence were complaints of some patients.

Table I shows the treatment given in 14 of the 16 cases. Also listed are the ages of the patients, the time of occurrence of the prolapse following the hysterectomy, and the results of the treatment given.

*Read before the Central Association of Obstetricians and Gynecologists at Louisville, Ky., on Oct. 23, 1947.

with breech presenting, apparently a normal individual. During the course of the day respirations became labored and she developed paralysis of the limbs and the abdominal muscles. Consultation was called, and a diagnosis of acute anterior poliomyelitis was made. The difficulty in breathing increased, and the patient was placed in a respirator. Her labor progressed rather rapidly and so did her complicating symptoms. Heart tones were good.

We knew that this patient could not be out of the respirator for any length of time; it was found that about a minute and a half were the most she could go on breathing without the use of a respirator. Dilatation came to completion but there were no expulsive efforts on the part of the patient because of the paralysis of the abdominal muscles. We, therefore, had to plan to deliver this woman outside the respirator within a period of not more than ninety seconds. We organized a crew of about ten people. Each one was assigned a very specific task, two to hold the legs, one to do the extraction, one to handle the forceps for the aftercoming head, one to clamp the cord, one to deliver the placenta, one for the intravenous Ergotrate. We arranged for someone to get spinal fluid and one for blood transfusion. However, by the time delivery of the baby was carried out in accordance with our plan, there was not sufficient time to carry out some of the other work. We got a live baby and the mother was hurried back into the respirator. She appeared a little better after the birth but within twenty-four hours she died from a severe form of bulbar paralysis. Our pathologist said that he had never seen such destruction of tissue as he saw in that patient. The infant survived. I saw the baby when he was 4 years old.

I thought it would be of interest to cite the unusually dramatic situation which challenged our management of this labor.

DR. TAYLOR (Closing).—The observation has been made that poliomyelitis is not a childhood disease any more but is becoming a disease of the adult population. Strangely enough, the Public Health authorities through some means are able to predict where an epidemic will be.

As to Dr. McCoogan's suggestion of increased metabolism and increased growth hormone having something to do with the problem, I do not know. Someone else will have to work that out. I would not do a cesarean section before anticipated death in these patients because there have been some cases that battled it out in a respirator for a few days and then finally made a complete recovery.

It is apparent that there is increased danger of poliomyelitis infection during pregnancy. However, you can reassure your young women that they have 999 chances out of 1,000 of missing the infection.

Dr. Baker, the neurologist from the University of Minnesota, came out to Denver to be of aid. He did not wait until patients showed signs of cyanosis and the respirations were difficult before doing a tracheotomy. He took all the bulbar cases that he thought were going to do poorly and did an elective tracheotomy and got a flow of oxygen into the patient before cellular destruction had taken place in the stem of the brain. His treatment will improve the prognosis in bulbar poliomyelitis.

The discussants have all emphasized how dangerous a disease poliomyelitis is during the last months of pregnancy.

are clamped, cut, and ligated. The uterosacral and transverse cervical ligaments fuse at their uterine attachment and do not appear as distinct structures, but as a single fascial attachment. It is frequently not advisable to attempt to remove the entire stump because of peritoneal adhesions. But the canal with its epithelial lining can be removed, leaving the remainder of the cervix to which the ligaments are attached. A portion of the peritoneum of the enterocele between the uterosacral ligaments is removed and the overstretched uterosacral ligaments identified. These ligaments are united by chronic No. 1 interrupted sutures. These sutures are carried as high toward the promontory of the sacrum as is possible, to approximate the peritoneum and musculofascial structures without causing undue tension. This step prevents a recurrence of the enterocele of the posterior cul-de-sac.

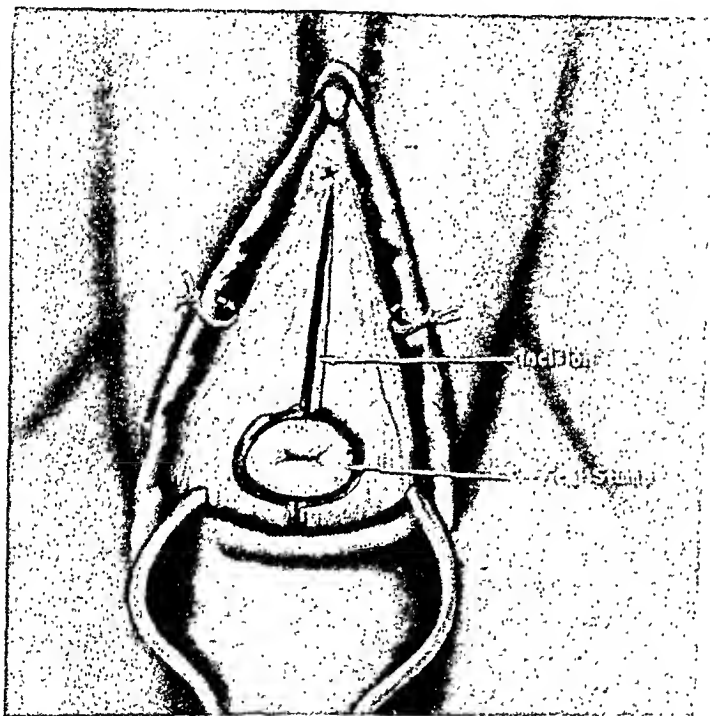


Fig. 2.—The everted vaginal wall is opened by a midline incision encircling the cervical stump.

The next suture (on a strong cutting-edge needle) is passed through the vaginal mucosa just beneath the attachment of the labia minora and carried into the periosteum of the pubis and then through the strong fascia structures lateral to the urethra. This suture then takes in the ligament stumps and passes through the sutured uterosacral ligaments, the peritoneum, and vaginal wall posteriorly. It is well to encircle the ligament stumps with a few stitches to secure hemostasis and prevent tearing out. A like suture is placed on the opposite side.

After these inclusive sutures are placed (but not tied), the fascia of the anterior vaginal wall (the pubocervical fascia), if discernible, is dissected from the vaginal wall flaps. In many of these cases, this fascia is somewhat fragmentary and cannot be sutured as a separate structure. When this is the case, all the structures in the vaginal wall are united as one layer in a single row of sutures. When the anterior vaginal fascia is adequate in amount and strength, it may be imbricated. If the patient has had urinary incontinence, the urethra

TABLE I. SIXTEEN CASES OF VAGINAL PROLAPSE FOLLOWING ABDOMINAL HYSTERECTOMY

| NUMBER | AGES | OCCURRENCE OF PRO- LAPSE AFTER HYSTERECTOMY | TREATMENT | RESULTS |
|--------|-------|---|----------------|---|
| 8 | 32-65 | 0-16 years | Plastic repair | 7 completely satisfactory 1 partially satisfactory |
| 4 | 62-68 | 1-15 years | Colpocleisis | Satisfactory |
| 2 | 67-69 | 5-12 years | Pessary | Relief |
| 2 | 49-67 | 0-10 years | None | |

In five of the cases observed, there was complete eversion of the vagina. In two of these cases, repair had been previously attempted and was unsuccessful. In eight cases, the operation employed was a plastic procedure utilizing the same supportive structures and following the same operative principles which are used by many pelvic surgeons in repair of genital prolapse at the time of vaginal hysterectomy.

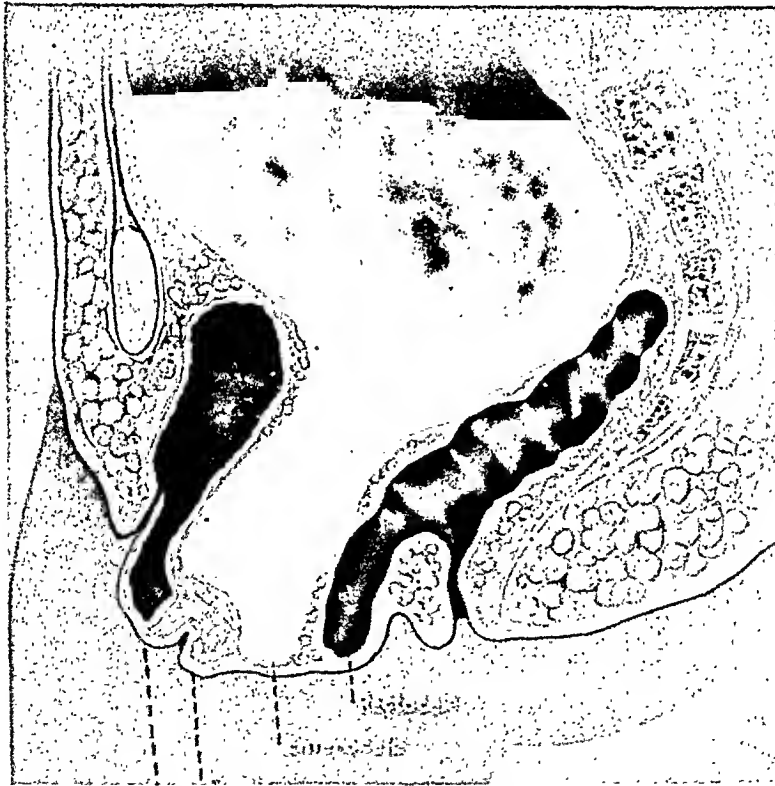


Fig. 1.—Prolapse of the vagina following subtotal hysterectomy.

Technique of Plastic Operation

The mucosa of the everted vagina is incised by a midline incision extending posteriorly from a point just below the urethral meatus and encircling the cervical stump. The vaginal mucosa with the underlying fascia is widely dissected from the bladder. The bladder is separated from the cervical stump with or without opening the peritoneal cavity anteriorly. The posterior end-de-sac is then opened. This is usually done very readily because of the protruding enterocele. The fascial attachment of the transverse cervical (cardinal, or Mackenrodt ligaments or parametrium), and uterosacral ligaments to the stump

is dissected free and a succession of mattress sutures taken, as is the usual procedure for the cure of incontinence.

The vaginal wall is sutured by interrupted sutures, before the inclusive sutures attached to the ligaments are pulled taut and tied. If the vaginal wall is sutured before the sutures attached to the ligaments are tied, more accurate approximation can be attained. This method of repair of vaginal prolapse is similar to that described by Heaney² and others for the correction of prolapse at the time of vaginal hysterectomy. The procedure appears to be particularly suitable for the cases of incomplete prolapse but may be inadequate for some cases of complete herniation of the vagina.

In four cases of complete vaginal prolapse in older women in whom a functioning vagina was of no concern, an occlusion operation of the Neugebauer-Le Fort type was performed. In every case, the results were very satisfactory.

In the material of this report, no abdominal operations were performed, although such procedures appear suitable for cases of complete prolapse in younger women in whom a functional vagina is desirable, especially if vaginal repair has been unsuccessfully attempted, or following complete hysterectomy, where the supporting structures appear to be inadequate for repair.

A perineorrhaphy should regularly be performed with any procedure for correction of this condition. It is important in doing the perineorrhaphy not to remove an extensive amount of vaginal wall because this will diminish the capacity of the vagina, which is unavoidably shortened by extensive plastic procedures.

Discussion

From a review of this small group of cases, it is likely that in many instances genital prolapse existed at the time the hysterectomy was performed, was unrecognized, and the operation selected was not adequate for its correction. However, this is not always the case. In some elderly patients, the loss of pelvic fat and atrophy of the pelvic supportive structures associated with advancing years permit prolapse of the vaginal vault which is not present at the time of hysterectomy. Occasionally, a large uterine tumor that cannot enter the true pelvis prevents prolapse of the uterus but, after its removal, prolapse of the cervical stump or vaginal vault occurs.

Anatomical studies of the supports of the uterus and vagina by Curtis and his associates³⁻⁵ and studies of the mechanics of uterine support by Menger⁶ have unquestionably shown that uterine and vaginal support in the main depends upon the integrity of the derivatives of the endopelvic fascia which is attached to the lower portion of the uterus, the cervix, and upper portion of the vagina. Uterine and vaginal prolapse is always the result of injury or congenital defect of these structures. They have been confused by nomenclature, but are frequently named the paravaginal fascia, the transverse cervical, and uterosacral ligaments. The paravaginal extension of fascia is so important that the vagina does to a great extent support the cervix rather than the cervix contributing to the support of the vaginal vault.

In most instances, prolapse of the cervix or vaginal vault following removal of the uterus is preventable. Clinical experience and anatomical studies have shown that suspending the cervix or vaginal stump by the round and infundibulopelvic ligaments, which are not supporting structures, following hysterectomy is a useless procedure. Suture of the anterior and posterior

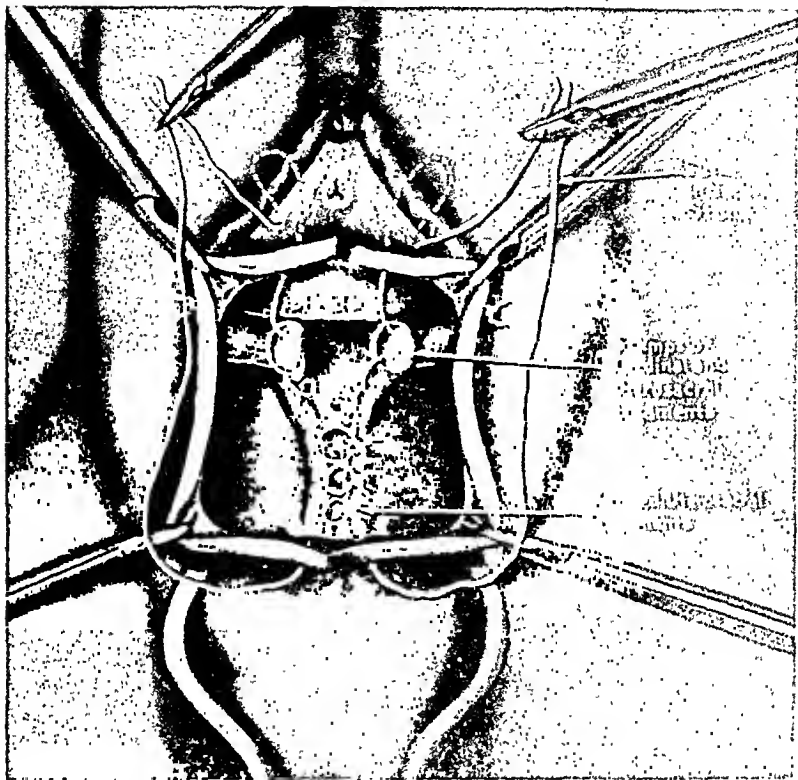


Fig. 3.—The cervical stump is removed. The fascial attachments to the stump have been ligated. The uterosacral ligaments are sutured together and a suture is passed through the vaginal wall anteriorly, the periosteum of the pubis, around the ligament stumps, and out through the posterior vaginal wall. This suture is tied after the vaginal mucosa is closed.

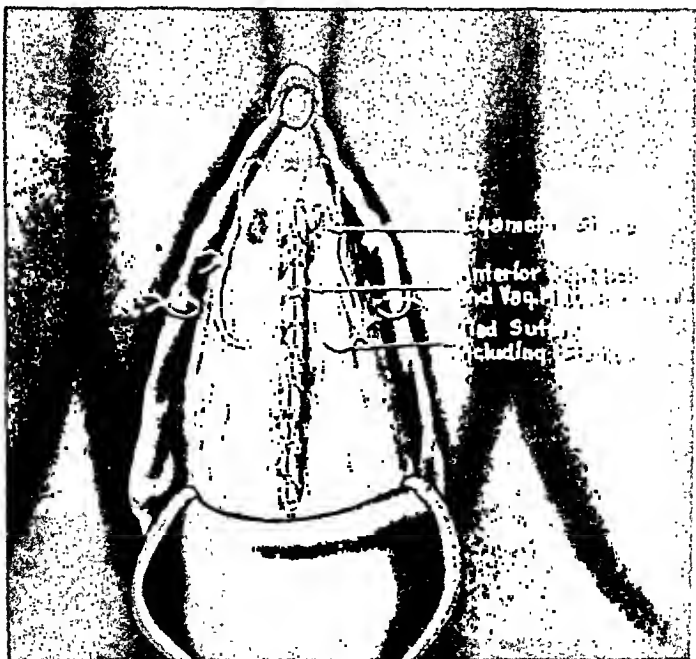


Fig. 4.—The pubocervical fascia and vaginal mucosa are sutured. The inclusive sutures attached to the fascial supportive structures are now tied.

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Discussion

DR. EDWARD ALLEN, Chicago.—The large number of new procedures reported in the recent literature is direct evidence of its frequent occurrence in the inadequacy of our varied techniques. A similar discussion and devising of new techniques is going on in the consideration of inguinal and femoral herniation. Many inguinal and femoral hernias are still recurring. The constitutional inadequacy of most of these individuals is well recognized. It is difficult to build a permanent water-tight dam out of secondhand lumber. Until we can build and breed more adequate structural supports into our adolescents and generally do better obstetrics, I fear we will have this problem continuously with us. Complete prolapse in the nullipara is strong circumstantial evidence to this fact.

It is very interesting that all of the patients observed by Dr. Bickel had been subjected to abdominal hysterectomy. Avoidance of this complication is one of the usual reasons given for removing the uterus through the abdomen. I should like to ask Dr. Bickel what percentage of these cases had evidence of vaginal repair other than episiotomy.

It is naturally a much more difficult procedure to secure adequate functional results in repair of a complete eversion of the vagina than it is when the herniation has occurred through a relatively small break in the fascial planes. The difficulties are increased considerably if scar tissue is present from a previous attempt at operation, although I believe some of our good results are due to causing scar tissue in the right place. The majority of the patients upon whom I have operated for this condition have had supravaginal abdominal hysterectomy without any, or with very inadequate, attempts at pelvic repair. However, this same condition existed in two patients in whom the uterus had been removed vaginally; the third patient had had the usual vaginal hysterectomy and repair. Again, this demonstrates a fact which we have all known for a long time, namely, one cannot successfully suspend the vaginal vault from above by attaching it to any of the intra-abdominal structures alone. As the author states, Curtis, Mengert and others have shown by anatomic and experimental studies the great importance of the parametrium which we call the cardinal and uterosacral ligaments and paravaginal fascia. One recognizes this fully during vaginal hysterectomy; when these structures are divided, increased mobility of even a greatly enlarged uterus immediately occurs. This increased mobility is frequently entirely inadequate to complete the hysterectomy until the vaginal canal is straightened out by depression of a high perineal body by a strong resident or Schuchardt's incision.

For many years, most of the men on our gynecologic service have, in marked prolapse or eversion, sutured the round ligament stumps high along the urethra in approximately the same position as Dr. Bickel has described. We have anchored them to the vaginal mucosa and para-urethral fascias but have not included the periosteum of the pubis. Generally the right ligament is sutured to the left angle and the left to the right, forming a sling. However, we have felt that the change in angulation produced in the vagina was more important than the building of a wall of tissue which is normally so mobile and so easily stretched. I venture a guess that the excellent results reported by Dr. Bickel were increased in part by a change in the angulation of the vagina when the posterior ligaments were drawn far forward rather than the fixation to the low level of the pubic periosteum. This drawing forward of the posterior supports should in a sense obliterate the cul-de-sac, which most of us feel is quite important in this type of repair. It is felt that this, as well as the high suture of the uterosacral ligaments, directed the downward thrust of the abdominal contents backward toward the hollow of the sacrum and strong upper levator sling rather than mere support from the lower margin of the symphysis pubis. However, Miller, in describing his repair operation, believes that stronger high sacroterine fixation will hold the vault of the

fascias of the vagina, which are extensions of the transverse cervical and uterosacral ligaments, aids in supporting the stump, but if the paravaginal fascia is intact, vaginal prolapse is not likely to occur if no attempt whatever is made to suspend the stump. If descensus is present at the time hysterectomy is contemplated, vaginal removal of the uterus and repair of the hernial defect is the procedure of choice. In cases of large uterine tumors associated with descensus, a combined vaginal and abdominal operation may be necessary.

When vaginal prolapse does occur subsequent to hysterectomy, it presents a surgical problem that is considerably more difficult than genital prolapse before the uterus has been removed.

From the number of surgical procedures which have been devised for the correction of vaginal prolapse, it is obvious that no single, or simple operation will give satisfactory results in every case. Vaginal occlusion operations have been used for uterine and vaginal prolapse for many years, but are suitable for only a limited number of patients. For elderly and noncohabitating women, it is a short and simple operation which usually gives very satisfactory results. In patients who are not good surgical risks, a partial or complete colpocleisis operation may be performed with local infiltration anesthesia. A vaginal operation has been devised by Miller⁷ which attaches the vagina high in the pelvis to the uterosacral ligaments. Other procedures which attach the vagina to the anterior abdominal wall have been devised by Brady⁸ and Ward,⁹ using silk sutures and ox fascia lata. More recently, an abdominal operation has been employed wherein strips of rectus fascia have been attached to the vaginal stump which reinvert the vagina. Satisfactory results have been reported.

Summary

Sixteen cases of vaginal prolapse following subtotal abdominal hysterectomy were studied. Prolapse of the cervical stump occurred within from less than one year of 16 years following the hysterectomy. No cases were observed following total abdominal or vaginal hysterectomy.

The treatment in 14 cases consisted of: a vaginal plastic procedure in 8 cases; colpocleisis in 4 cases; and 2 cases were treated by wearing a pessary.

A study of the anatomy and mechanics of uterine and vaginal support and also clinical observation demonstrate that removal of the cervix with the fundus of the uterus does not predispose to prolapse of the vagina.

When uterine descensus is present at the time of hysterectomy, vaginal removal of the uterus and repair of the hernial defect will prevent subsequent prolapse of the vagina.

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TREATMENT OF URINARY TRACT INFECTIONS WITH SULFATHALIDINE (PHTHALYLSULFATHIAZOLE)*†

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THE treatment of urinary tract infections has always been a matter of some concern. This is evidenced by the multiplicity of methods: acidification, alkalinization, urinary antiseptics, sulfonamides, and antibiotics. With the development of specific drugs, it was hoped that the treatment would no longer be a problem. This is quite true in the great majority of uncomplicated acute infections. Cook has stated that 90 per cent of such cases can be cured with one of the sulfonamides.¹ Penicillin has been of considerable help in complicated cases where most sulfonamides cannot be used safely because of toxicity or sensitivity. However, this antibiotic has failed to be of value in infections caused by the colon-typhoid group of organisms. Streptomycin has a supposed specific action on these organisms. However, it is contraindicated in pregnancy because of the possible injury to auditory and vestibular nerves.² There are some urinary infections that do not respond, and others that have a tendency to recur.

It is the urinary tract infections caused by *Esch. coli* that aroused our special interest. Many acute infections with this organism respond to sulfadiazine or sulfathiazole, but the chronic cases often are not affected. In complicated cases occurring during pregnancy or postoperatively, one must use these drugs with considerable caution. Thus it is necessary to find a compound which will cure urinary infections of *Esch. coli* in both acute and chronic cases and which will be sufficiently nontoxic to allow its use in cases with complications such as impaired renal function, severe anemias, pregnancy, etc.

With this in mind, Everett and his co-workers³ studied the use of sulfasuxidine in such cases and found it to be of considerable value. This drug had been used in gastrointestinal surgery to reduce the *Esch. coli* content of the bowel. It was found by Poth and his collaborators^{4, 5} at Johns Hopkins University that only 5 per cent of the drug was excreted in the urine. Blood levels were never more than 1.5 mg. per cent of sulfathiazole and 2 mg. per cent of stecinylsulfathiazole (sulfasuxidine). Because of its scanty absorption and low toxicity, sulfasuxidine is well tolerated even in complicated cases. However, Poth,⁵ Clay and Pickrell,⁶ and Johnson⁷ reported several unfavorable reactions, one of which was a case of fatal agranulocytosis. Most of the reactions were said to be due to a sensitivity or idiosyncrasy to sulfathiazole. Everett³ stated that his chief objection to the drug was its expense due to the large dosage required.

*The Sulfathalidine used in this study and funds for this study were supplied by Sharp & Dohme, Inc.

†Read before the Central Association of Obstetricians and Gynecologists in Louisville, Ky., on Oct. 25, 1947.

prolapsed vagina in its elevated position. Dr. Bickel has indicated the similarity of the placement of the fixation suture to the one usually used to close the outer corners of the incision for vaginal hysterectomy. He has also stressed the need for adequate posterior repair as a most important part of this procedure.

The vast majority of all of the patients upon whom I have operated for procidentia, and especially those in whom recurrences have happened or who have come to me for secondary repair, have been fat women, many of them with an abnormal bacterial flora in the vagina. It seems to me these factors are just as important as they have been proved in breakdown of the abdominal scar. Many of my best results in secondary repair have been in those patients in whom weight reduction, improvement in resistance, and curing infection in the vagina have preceded the operation; my poorest results when they have not been corrected. I believe the cervical stump can usually be safely and completely removed and should be on account of the risk of stump carcinoma.

DR. PAUL FLETCHER, St. Louis, Mo.—We have seen seven cases of complete prolapse of the vagina in seven years. In two of these the cervix was present, in the others removal had been complete. In each case the original operation had been done by some one other than a trained gynecologist. In all of our cases, previous attempts had been made to repair the prolapse.

I would like to ask Dr. Bickel in how many of his cases a previous attempt had been made to correct the prolapse.

DR. BICKEL (Closing).—In two of the reported cases, unsuccessful attempts at repair had previously been made; both were cases of complete vaginal prolapse. These cases might have been suitable for Dr. Fletcher's operation. It is unlikely that any of the cases reported had episiotomy and repair at the time of their deliveries.

I mentioned passing a suture through the periosteum. This is usually attempted but not always accomplished and is not essential. But in attempting to pass the suture through the periosteum, one does necessarily include the strong fascial structures lateral to the urethra which play an important part in the supporting mechanism.

other twenty cases had various other bacterial invaders. The types of cases with *Esch. coli* infections, along with the immediate results of treatment, are noted in Table I.

TABLE I. TWENTY-SEVEN CASES WITH URINARY INFECTIONS OF *ESCH. COLI* TREATED WITH SULFATHALIDINE

| CASES ASSO- CIATED WITH | PYELITIS | | CYSTITIS | | TOTAL | IMMEDIATE RESULTS AFTER TREATMENT | |
|-----------------------------|----------|---------|----------|---------|-------|--------------------------------------|---------------|
| | ACUTE | CHRONIC | ACUTE | CHRONIC | | SYMP. CURE | BACT. CURE |
| Pregnancy | 2 | 4 | 9 | 0 | 15 | 13 | 12 |
| Gynecological Conditions | 0 | 0 | 8 | 4 | 12 | 14 | 14 |
| Total | 2 | 4 | 17 | 4 | 27 | 27 | 26 |

The majority of the cases were treated with sulfathalidine for one to two weeks. However, since five persons did not return as directed, more drug was given because of the interruption of treatment. Four of the latter had three weeks' treatment and the fifth, four weeks. The routine of treatment was 6 Gm. per day, divided into 6 equal doses every four hours, for the time of hospitalization (approximately one week), and 4 Gm. daily for the ensuing time. Eight cases, two of which had chronic infections, were treated with 2 or 3 Gm. daily. There was no difference in the response of this latter group and that of the group treated with a larger amount of drug.

No patient received more than 6 Gm. daily, or approximately 0.1 Gm. per kilogram of body weight. The total amount of drug given to each patient varied from 27 to 86 Gm.; however, most of the patients received 42 to 72 Gm., or an average of 53 Gm. This compares very favorably with the amount of succinylsulfathiazole necessary to obtain comparable results. Everett used 0.25 Gm. of succinylsulfathiazole per kilogram per day for one week and another 0.125 Gm. per kilogram for one to two additional weeks. For a person of 60 kg., this is probably a total dosage of 157 to 210 Gm. of sulfasuxidine, or approximately three and one-half times the total dose of sulfathalidine.

The first culture taken after treatment of each case of *Esch. coli* was negative. After treatment was begun, negative cultures were obtained in fourteen or 50 per cent within the first week, and seven or 27 per cent within the second week; an over-all total of 21 or 77 per cent within two weeks or less. Unfortunately, some of the patients were discharged from the hospital in a very short time, so that in thirteen cases or approximately 50 per cent, including the above-mentioned seven or 27 per cent, the first control culture was taken later than one week after treatment. Also, since most of the patients were treated in the clinic, it was not practical to obtain cultures other than at weekly intervals. In one case, the specimen contained *Esch. coli* after the second week of treatment. This occurred just before delivery in a patient having ureteral block; however, with no additional treatment, there was a negative culture after delivery two months later. After two weeks' rest from the drug, another patient had a recurrence which was cured permanently with ten days of treatment.

There were four mixed infections of *Esch. coli* and *Staphylococcus albus* or an enterococcus, all of which were cured of the bacilli with sulfathalidine. One of the cases of staphylococcus infections cleared without additional treatment and the other was cured with penicillin. The enterococci were eradicated with mandelic acid but reinfections occurred.

Everett advances two theories as explanation for the cure of urinary infections by this scantily absorbed drug. Succinylsulfathiazole itself has little "in vitro" value. However, some of the drug hydrolyzes in the body to succinyl acid and sulfathiazole or other similar compounds. Either this small amount of free or "split" drug excreted in the urine is enough to render it sterile or else the tissues of the urinary tract are allowed to rid themselves of infection when the source of contamination in the bowel is temporarily eliminated.

Sulfathalidine (phthalylsulfathiazole), like sulfasuxidine, is a member of the N⁴-carboxyacyl-sulfathiazole family. It has also been found to act in vivo in a manner similar to sulfasuxidine. About 90 to 95 per cent of the drug remains in the gastrointestinal tract. Poth and Ross⁸ found that in a dog receiving 0.5 Gm. per kilogram per day, the bacterial count fell from 10,000,000 to less than 10 per Gm. of wet stool in six days. As indicated by the alteration of the coliform flora in the bowel of man, phthalylsulfathiazole, in half the dosage, is as effective as succinylsulfathiazole.⁹ Poth also found that the maximum concentration of the conjugated drug (phthalylsulfathiazole) in the blood, with a dose of 1.0 Gm. per kilogram of body weight per day, has not exceeded 3.3 mg. per cent. Streicher¹⁰ has found that, irrespective of the dose, the concentration of sulfathalidine in the blood stream of human beings ranges from 0.5 to 1.5 mg. per cent. Poth and Ross⁹ report that approximately 5 per cent of the orally administered therapeutic dose is excreted in the urine. Crystals have not been observed following oral administration of the drug. This is due to the fact that the free form is not excreted in large quantities and because the conjugated drug forms soluble salts even at a pH of 5.6. Thus it may be seen that high bacteriostatic concentrations are readily produced and maintained within the bowel, that blood levels are clinically insignificant, and that drug crystalluria or renal obstruction has not been observed.

Poth and Ross⁸ reported that no toxic reactions had been demonstrated in dogs receiving oral doses of the drug. Intravenous injections caused vomiting at first but did not occur on further injections. There have been few toxic reactions seen in human beings. The same authors⁹ reported headache, nausea without vomiting, and fever in one woman who had developed the same reaction to sulfasuxidine. She was obviously sensitive to sulfonamides. These workers warn that as more persons receive the drug, it can be expected that more toxic manifestations will be seen; however, such reactions will be relatively infrequent.

Methods and Results of Study

The patients reported herein were those having a urinary infection as a complication of some gynecologic surgical procedure or of pregnancy. The diagnosis, initially made from signs and symptoms and by microscopic examination of a catheterized specimen of urine, was confirmed by culture.

The first culture was made before therapy was begun. In most cases, cultures were repeated at the end of the first week's treatment and subsequently every week until negative. Additional cultures were made every second week for several months.

Cultures were managed as follows: After centrifugation of the specimen, the sediment was streaked on a heart infusion agar with 1 per cent filtered lactose and an indicator of bromthymol blue. For the growth of anaerobes, particularly streptococci, two loopfuls of sediment were inoculated into recently heated thioglycollate broth with methylene blue indicator. All organisms which grew during incubation of these media at 37 degrees for two days were identified.

There were a total of 47 cases treated with sulfathalidine. *Esch. coli* was the organism involved in 27 cases. Four of these had mixed infections. The

TABLE III. URINARY INFECTIONS WITH ORGANISMS OTHER THAN *ESCH. COLI*

| ORGANISM | TYPE OF INFECTIONS | | | | | |
|-----------------------------|--------------------|----------------|----------------|--------------|----------------|----------------|
| | ACUTE | | | CHRONIC | | |
| | NO. CASES | SYMP. CURES | BACT. CURES | NO. CASES | SYMP. CURES | BACT. CURES |
| <i>Staphylococcus</i> | 5 | 5 | 5 | | | |
| <i>Streptococcus</i> | 3 | 3 | 2 | | | |
| <i>Aerobacter aerogenes</i> | 1 | 1 | 1 | 4 | 0 | 0 |
| <i>Alkaligenes</i> | | | | 2 | 2 | 0 |
| Mixed | 4 | 4 | 3 | 1 | 1 | 1 |
| Total | 13 | 13 | 11 | 7 | 3 | 1 |

The acute cases due to staphylococci or streptococci were cured of their infection but the chronic ones were not. There was a striking failure of the drug to influence the condition in cases infected with *Aerobacter aerogenes* and *Alkaligenes fecalis*. This was also noted by Everett in his work on sulfasuxidine. Nevertheless, all cases except four which were infected with *A. aerogenes* improved symptomatically.

As a control of the drug, seven cases of *Esch. coli* and seven other infections were treated with sulfadiazine. The sulfadiazine was given only while the patients were at the hospital; so treatment varied from three to fourteen days. All cases of colon infections were acute and were cured. Of the other infections, two acute cases of staphylococcus and streptococcus were cured, one paracolon pyelitis was cured temporarily, but four cases of *A. aerogenes* or *Alk. fecalis* were not cleared of their infections. Three of these failures were improved symptomatically, however.

None of the patients showed evidence of toxicity or reaction from the sulfathalidine. One patient had been given four weeks' continuous treatment with sulfathalidine in a test of the value of the drug against enterococcus infection. After a month's rest, she was given another two weeks' treatment. There was no sign or symptom of toxicity with this long treatment. Another case had had the left kidney removed and now had pyelitis of the right kidney. This person received treatment for thirteen days when she began to vomit following ingestion of the medicine. She was later treated for seven days without any untoward reaction. It was very questionable that the medication was the cause of her nausea.

Discussion

Most uncomplicated, acute, urinary tract infections can be controlled by use of the sulfonamides. However, chronic cases, especially those due to *Esch. coli*, often resist all forms of therapy. With sulfathalidine, we have been able to cure both acute and chronic urinary tract infections due to colon organism. Even where there was a mixture of organisms, the colon bacilli were eradicated. The effectiveness of the drug is made evident by the short time necessary to obtain negative cultures and by the long period of negative cultures after cessation of treatment. The prompt cure of chronic cases which had previously resisted other therapy also attests to the value of sulfathalidine in *Esch. coli* urinary tract infections.

It was interesting to find that five cases of acute staphylococcal cystitis and two of three cases of acute streptococcal cystitis were cured symptomatically and bacteriologically with sulfathalidine.

Table II shows the number of cases which were observed for varied periods. It may be seen that eight cases, followed for two months, and fourteen cases, followed for three months to one year after the time of treatment, were cured symptomatically and bacteriologically.

TABLE II. TIME CASES WERE FOLLOWED AFTER TREATMENT

| TIME | BACTERIOLOGIC AND SYMPTOMATIC CURES | INCOMPLETE TREATMENT | REINFECTIONS |
|--|--|-------------------------|--------------|
| 2 months | 8 | | |
| 3 months | 3 | | 1 |
| 4 months | 2 | 1 | |
| 5 months | 2 | | |
| 6 months | 4 | | |
| 7 months | 1 | | |
| 8 months | 1 | | |
| 1 year | 1 | | |
| Immediate cure but no follow-up after treatment | 3 | | |
| Total | 25 | 1 | 1 |

There was only one case of reinfection with *Esch. coli*. This appeared three months after the original treatment. However, there were four cases of reinfections with other organisms after the *Esch. coli* was eliminated. Three of these were *Aerobacter aerogenes* and one was *Alkaligenes fecalis*.

Case Reports

Mrs. F. L., aged 24 years. This patient developed acute cystitis after an abdominal hysterectomy in December, 1944. She was known to have a right ureteral stricture and was under the care of a urologist prior to surgery. Cultures taken in the hospital were positive for *Esch. coli*. The patient was known to be quite sensitive to sulfathiazole and was given sulfacetamide with poor results. Mandelic acid was also tried but not successfully. On Jan. 3, 1945, she was given 2 Gm. sulfathalidine for the first dose, and 2 Gm. daily thereafter for fourteen days. On January 9th, six days later, the urine was free from pus cells, and the patient was symptomatically cured. No further trouble took place. Subsequent urine cultures were negative for *Esch. coli*.

Miss B. F., aged 40 years. This patient had a chronic pyelo-cystitis, which began in October, 1945. Cultures were positive for *Esch. coli* at this time. The patient was treated by a urologist in October and November, 1945, with sulfacetamide, but with poor results. In January and February, 1946, she had severe right kidney pain and was treated with penicillin, but the urine continued to contain pus and *Esch. coli* organisms. In March, 1946, the urine showed many pus cells and the pain in the right kidney region returned. In April, 1946, when there was a recurrence of pain and positive cultures, the patient was put on mandelic acid by the urologist, but again the results of treatment were poor. On Dec. 16, 1946, the patient had another recurrence of kidney infection with a positive culture for *Esch. coli*. At this time she was put on sulfathalidine, 2 Gm. immediately and 2 Gm. daily for fourteen days. On December 19th, three days later, symptoms were much improved and there was a marked decrease in the number of pus cells in the urine. On December 23rd, there were very few pus cells, and on February 13th, the urine culture was sterile. It was sterile also on March 6, 1947. Since the recrudescence in December, 1946, there has been no return of symptoms. The last urine culture on August 6th, eight months after treatment, was negative.

It has been mentioned that 20 other cases of various types of infections were treated. The same routine of treatment was used for these as for the patients having *Esch. coli* infections. Table III shows the results of treatment of these cases.

7. Sulfathalidine can be used where other sulfonamides would be contraindicated because of its poor absorption and low toxicity. This is especially true in pregnancies complicated by impaired kidney function or severe anemia.

8. The dosage necessary to bring about a cure was 0.1 Gm. per kilogram of body weight daily for an average of two weeks. Eight cases were given 0.05 Gm. per kilo.

9. Due to the low dosage required, the cost of the drug does not make its use prohibitive in the low income group.

10. Its mode of action is most probably similar to that advanced by Everett and his co-workers for sulfasuxidine.

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It was also noted that, like sulfasuxidine, the drug had little effect on urinary tract infections due to *Aerobacter aerogenes* and *Alkaligenes fecalis*.

We agree with Everett that the most probable mode of action of both sulfasuxidine and sulfathalidine is twofold. The elimination of the foci of infection in the bowel apparently gives the urinary tract tissues time to combat the infection through their own resistance; moreover, the "beneficial effect exerted on the intestinal tract may decrease the avenues of escape of organisms into the blood stream or lymphatic channels through which they may have been reaching the urinary tract." We also feel, however, that there is some definite sensitivity of *Esch. coli* organisms to this particular type of sulfonamide or to its products in the body.

As in the case of sulfasuxidine, the lack of toxicity of sulfathalidine is a factor which allows treatment in conditions such as impaired renal function and severe anemias. These conditions are often found during pregnancy, and ordinary sulfonamides would be contraindicated.

With sulfathalidine there was not the objection of high cost of the drug due to large amounts required, as found by Everett. Whereas he found it necessary to use an average of 0.25 Gm. of sulfasuxidine per kilogram daily for one week and half this amount daily for a second week, we were able to accomplish similar results with an average dose of 0.1 Gm. thalidine per kilogram daily for one to two weeks. In eight cases, a smaller dose, 0.05 Gm. per kilogram, was used with excellent results.

As is expected with acute infections, average doses of sulfadiazine gave good results in seven cases of acute cystitis caused by *Esch. coli*. However, four cases of *A. aerogenes* and *Alk. fecalis* infections failed to respond to this drug.

Streptomycin has been reported as being efficacious for *Esch. coli*, but there have also been reports of auditory and vestibular nerve injuries from this antibiotic. Therefore, we would be hesitant to use streptomycin during pregnancy and recommend sulfathalidine as the therapeutic agent of choice.

Summary and Conclusions

1. We have used phthalylsulfathiazole successfully in the treatment of acute and chronic urinary tract infections due to *Esch. coli*.

2. Chronic cases of *Esch. coli* that were resistant to other sulfonamides, penicillin, and mandelic acid were cured bacteriologically with sulfathalidine.

3. Twenty-six out of twenty-seven cases of *Esch. coli* infections were cured symptomatically and bacteriologically.

4. Negative cultures were obtained in 50 per cent of the cases in one week or less and in 77 per cent in two weeks or less.

5. The first culture taken after treatment (which, in twelve cases, was after the first week) was negative in all cases.

6. Sulfathalidine did not seem to have any effect on cystitis caused by *Aerobacter aerogenes* or *Alkaligenes fecalis*. It did have some effect on urinary tract infections caused by staphylococci and streptococci.

The increment between 280 and 300 days is about 130 grams. Thus it would seem that placenta size is more significant in determining the size of the baby than is postmaturity of some three weeks' duration in the proportion of about 7 to 1.

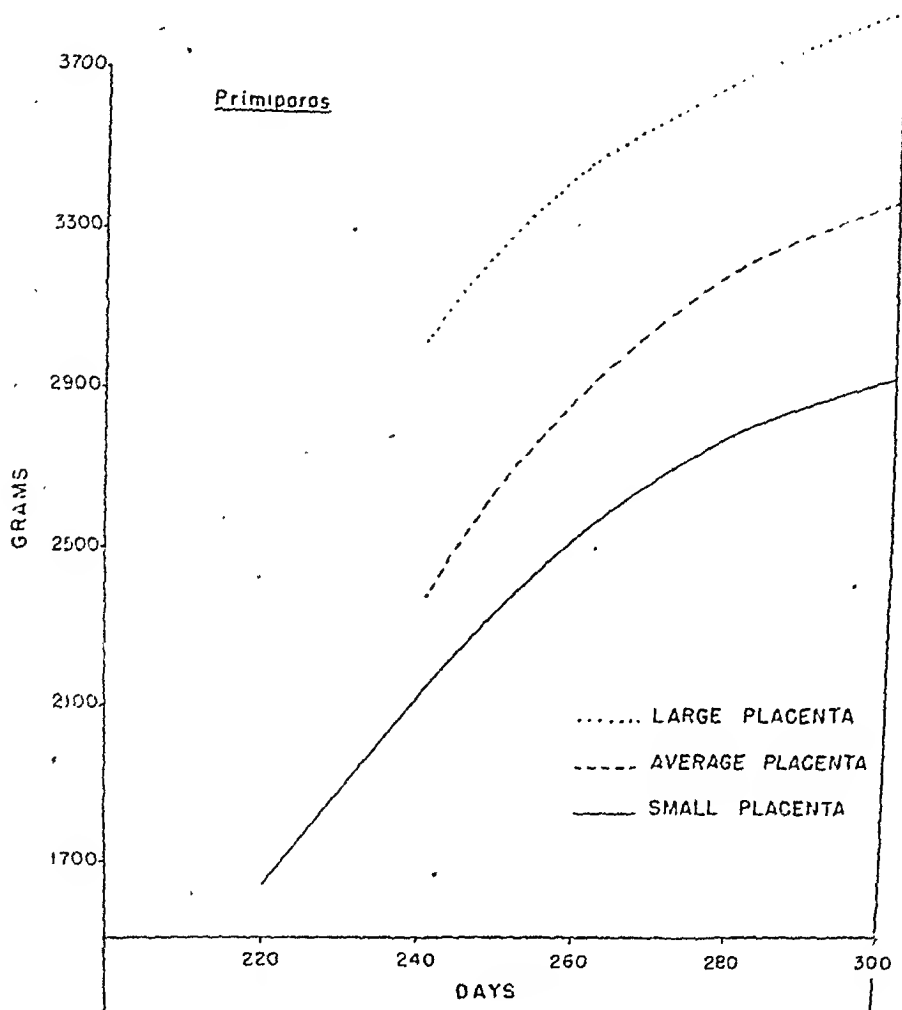


Fig. 1.

Even more striking is the fact that in the primiparas, eight patients whose pregnancy exceeded 295 days and whose placentas weighed 400 grams or less had infants not exceeding 3,000 grams in weight. On the other hand, in nine patients with a pregnancy of 264 days or less and with placentas weighing 700 grams or more the *average* weight of the baby was 3,560 grams.

From the foregoing, it is quite apparent that if an infant is to be oversize at full term, it will have acquired most of that excessive size by about the two hundred sixtieth day of the pregnancy. It is, therefore, important in those patients where the size of the infant may be a complication to recognize that large size early. On the other hand, if the infant is large at full term, its further increment in size thereafter will be so little that it will make no real

POSTMATURITY*

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MANY years ago, Dr. Rudolph Holmes stated that there was no problem in postmaturity. Textbooks continue to suggest, however, that labor may be more difficult in patients going well past their due date by virtue of the increased size of the baby and the lessened possibility of molding of the more ossified head. Williams and others have, however, consistently advised against induction of labor in order to avoid these possible difficulties.

As far as we have been able to determine from the literature, no one has ever accurately proved that postmature babies are larger, and if so, by how much. Nor has anyone actually determined, except in isolated case reports, that the postmature heads are less well molded in the birth process.

In a recent rather careful study of the size of placentas at the various stages of pregnancy and the correlation of placenta size with infant size, some very interesting data were developed. It was found that the growth curve for both placentas and babies follows the general form of the elongated S so characteristic of all mammalian growth. Increase in size continues throughout the pregnancy, but contrary to the impression given by the Hasse formula and other estimates of growth (except the Seammon-Calkins formula), this growth is not at a uniform rate. In the case of the placenta weight and the baby weight, growth is rapid up to about the two hundred sixtieth day. It is much less rapid from the two hundred sixtieth to the two hundred eightieth day, and the increment after full term is reached is very small (Figs. 1 and 2).

If one divides the material into three groups, according to whether the placenta weighs less than 500 grams at the time the baby is born (wet weights), from 500 to 695 grams, or 700 grams and above, some very interesting results are obtained. The average weight of primiparous babies with small placentas at full term (270 to 289 days) is 2,810 grams. With placentas between 500 and 695 grams, the baby weight is 3,295 grams; with large placentas it is 3,675 grams. Thus the span between small and large placentas is *on the average* 865 grams. Compared with this, the increment between 280 days and 300 days is only 120 grams or less. Similar figures for multiparas are as follows:

| PLACENTA SIZE | DAYS GESTATION | SIZE OF BABY |
|--------------------|----------------|--------------|
| Under 500 grams | 270 to 289 | 2875 grams |
| 500 to 695 grams | 270 to 289 | 3310 grams |
| 700 grams and over | 270 to 289 | 3795 grams |

Here the difference in baby size between small and large placentas is 920 grams.

*Read before the Central Association of Obstetricians and Gynecologists, Oct. 23, 1947, Louisville, Ky.

I, along with many, many others, have been guilty in the past of using low forceps much more commonly with the large babies than with the small because it was felt that the second stage "would be prolonged." Unduly prolonged second stage will occur in the presence of a large baby and poor pains, but only in 5 per cent or less of patients who are not too heavily medicated, and thus cannot be offered as a reason for doing forceps deliveries on 50 per cent or more of all primiparas, more than half of whose babies will be small.

There is no doubt that ossification is going forward in the latter part of pregnancy and that this process continues after delivery. Rather extensive studies of the closure rate of both suture lines and fontanels throughout the period of infancy and early childhood are now available. Obviously a baby born as much as two months postmaturely would have some definite increase in the rigidity of its cranial vault. In this present series of 6,000 cases, there was only one patient whose pregnancy exceeded 316 days, and the vast majority of the "postmature" group were delivered at the end of 305 days or less. Thus the problem is one of two or three weeks' postmaturity, not one of two or three months. In this two or three weeks the amount of increased ossification is certainly negligible so far as creating a problem for the average patient.

It would seem safe to agree with Dr. Rudolph Holmes that there is no postmaturity problem.

Discussion

DR. GEORGE KAMPERMAN, Detroit, Mich.—This presentation on postmaturity has not in any way changed my conception or reasoning on the problem, for my attitude toward this question quite corresponds with that of the essayist.

Dr. Calkins begins his presentation with an assertion by Rudolph Holmes and ends it with an endorsement of that same opinion. In his discussion he presents research data to uphold the contention that the size of a baby depends on the size of the placenta, rather than on a short period of postmaturity.

My recent encounter with the postmaturity question has been as an executive in a very active obstetric division. As such it was always my attitude to watch over the type of obstetrics practiced and especially to try to throw influence against any too radical type of procedure. I was impressed by the fact that cases of postmaturity caused no worry and presented no problem to most of the staff members. It seemed that the indication to induce labor in cases of delayed labor was present in the practice of only a couple of men. It seemed strange that this should occur thus, and I often wondered whether so-called postmaturity was not a state of mind of the obstetrician rather than an actual occurrence.

This problem came to a head somewhat during World War II when scarcity of hospital beds resulted in a rule that the hospital could furnish no beds for patients who were not actually in labor unless some recognized complication existed. This at once put an end to the induction of labor for postmaturity, much to the relief of the entire staff and especially to those who had been accustomed to inducing labor for this indication. One does not need a great experience with attempted induction in cases of postmaturity to learn soon that it is much easier and simpler to allow patients to go into labor spontaneously than to induce labor and have to be on call rather closely during the period of induction—at times quite a prolonged period.

We might ask the question, Is there such a condition as postmaturity? Obstetric literature is rather deficient in discussions on this subject. It probably means that in most clinics

difference in the course of the subsequent labor. The obvious disadvantages of inducing labor in the presence of an unprepared cervix cannot possibly be justified on the basis of this small increment in the postmature baby.

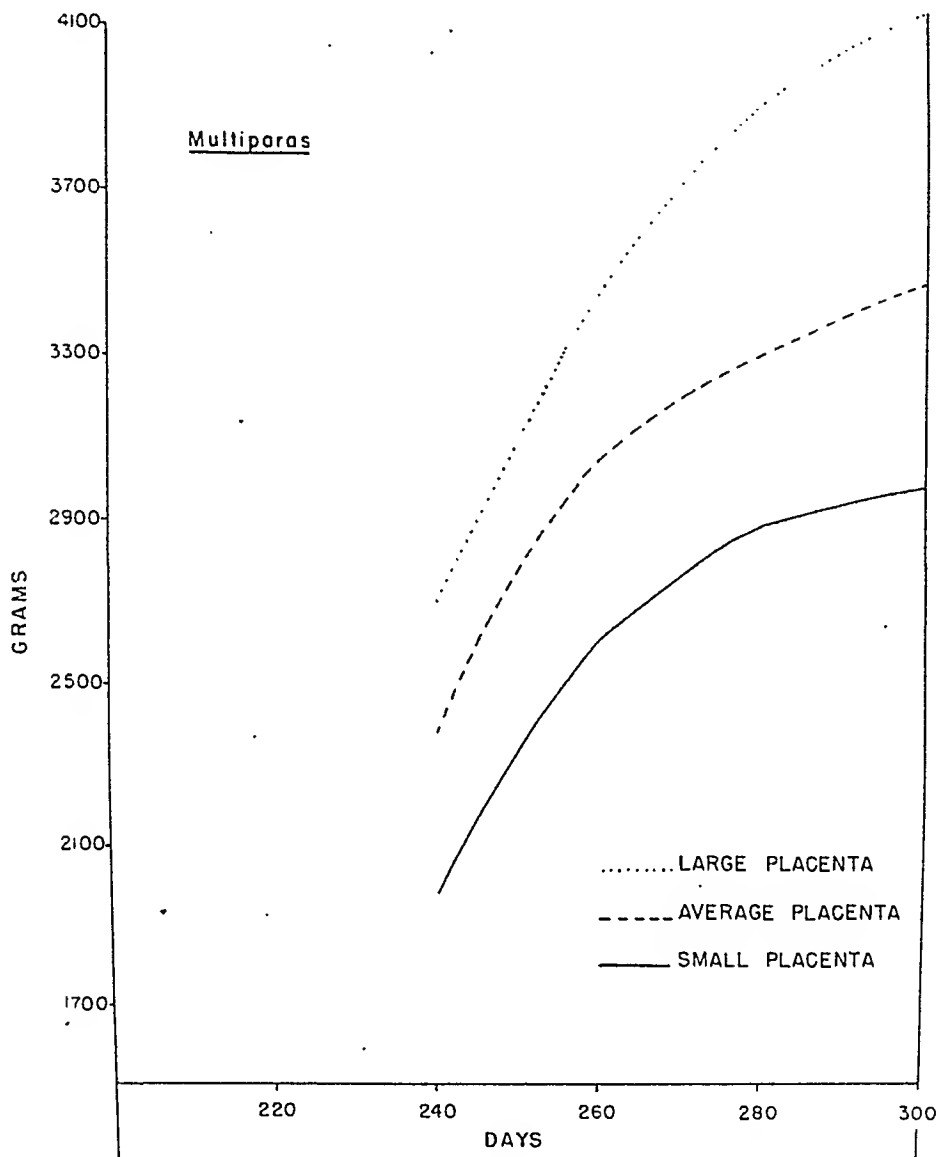


Fig. 2.

We have pointed out in a previous publication that the first stage of labor is no longer with large babies than it is with small ones. We have also pointed out that the second stage of labor in primiparas is slightly longer (by about six minutes on the average) where the baby is large. More recent, and as yet unpublished studies, would indicate that this small difference is physiologic rather than anatomic in nature. It seems that the labor pains in the second stage have a tendency to be poorer with the large babies. Perhaps this is just as well. The additional six minutes (and the two or three extra labor pains involved) may produce less trauma to the birth canal and less frequent injury to the child.

DR. JACOB L. BUBIS, Cleveland, Ohio.—In contradiction to Dr. Holmes, there is such a thing as postmaturity. I want to report the case of a woman, aged 37 years, who had two children aged 7 and 6 years. On April 14, 1946, I performed a dilatation and curettage, perineorrhaphy, and hemorrhoidectomy on this patient. Three months later she had an attack of appendicitis which cleared up. I next saw her on Jan. 22, 1947. Her last menstrual period had occurred on December 9, and examination showed the uterus three fingers above the pubis. Her expected due date was Sept. 16, 1947. The patient reported to me regularly. At the time of her due date I did not want to aggravate the appendicitis by giving castor oil, so I let her continue. On October 14 she went into spontaneous labor and had a baby of moderate size; the cord was small and very thin and almost pulseless, and the skin was peeling from the hands, head, and body. The baby cried spontaneously but weakly. It was apathetic for several days. Since then the skin has healed completely; he takes his nourishment well and has gained in weight. However, the muscles of the arms and legs are weak and the pediatrician states that the infant has symptoms suggesting myasthenia gravis. I am quite sure this is a case of postmaturity for the records.

DR. CHARLES GALLOWAY, Evanston, Ill.—I would like to ask the essayist a question because I do not know the answer and maybe some of the others do not know it either. What about death and overdue babies? What about the patient who goes three or four weeks beyond the calculated due date and then one day shows up without fetal heart tones, or goes into labor and the baby dies during labor without any cause that one can find? Does that condition exist?

DR. CALKINS (Closing).—I always forget to give certain points in my presentations. These 6,000 patients included in this series were in a sense selected patients in that the whole series comprised something like 9,000 cases, and in 3,000 the histories of the last menstrual period were not considered sufficiently accurate. Those were, therefore, thrown out. We thought the histories in these 6,000 cases could be depended upon as being reasonably accurate and that any individual inaccuracies would be overcome by the fact that part of them would be in one direction and part in the other and would be compensatory. I am well aware of the fact that menstrual histories cannot be depended upon, but I am also quite certain that in some of the patients they can be depended upon. In a good many of these particular patients we know the histories are accurate because we saw the patients in the first month or six weeks of pregnancy and know there could be no serious inaccuracy.

Dr. Galloway has raised a question. I do not think any of us know the complete answer. We have seen this type of thing and there was one such baby in this series. However, during that same period of time we had six or eight similar stillborn babies in women delivered at full term or before full term. Dr. Galloway described a situation in which he cannot accurately ascertain the cause of fetal death, and we have had several similar patients in which this occurs in the premature group.

Dr. Kamperman made reference to the fact that the baby may get smaller if it gets sufficiently postmature. That seems hardly likely and does not obey any of the rules of growth. We noted in this series that postmaturity was much more frequent when the placenta was small and much less frequent when the placenta was large. It would, therefore, naturally follow that if one should get the weights and pay no attention to the placenta, he would get a large percentage of small babies in the postmature group and would thereby have the average postmature baby's weight reduced.

the problem is not considered important enough to deserve much study. Rathbun, in 1943, discussed the problem as it occurred in the Boston Lying-in Hospital. He classes as postmature those pregnancies where labor does not occur before 295 days after the first day of the last menses. This allows 15 days beyond what is usually considered the estimated date of delivery. In his 250 cases the statistics do seem to show a somewhat larger baby if the pregnancy goes overtime, a slight lengthening of labor, and a slight increase of interference necessary in delivery, especially of the more major types of interference. Analyses showed no increased fetal mortality that could be accredited to postmaturity. There was no increase in intrauterine fetal deaths. Masters and Clayton, reporting from England, revealed that in cases of postmaturity there was no more excessive calcification or degeneration of the placenta than in normal mature cases. They found nothing in placental study to lead one to think that intrauterine death had any relationship to postmaturity.

We might infer from Rathbun's report that there is such a condition as postmaturity. However, the series is small. What is lacking in the literature is a reported series large enough to give conclusive and convincing deductions. We have all seen so-called overdue patients with large babies but also some with small babies, and both observations hold true for patients not overdue.

But even though one might admit that postmaturity is occasionally genuine, yet it seems doubtful that it ever presents much of a problem.

Strangely enough, statistics seem to show that if a baby goes postmature beyond twenty days it begins to lose weight. So then if we estimate that prematurity does not exist until the pregnancy goes 15 days beyond the estimated date and then if the baby will begin to decrease in weight five days later, there should be little worry about excessive gain in the baby's weight. Statistically the longer postmaturity continues after twenty days, the smaller will be the baby. Furthermore, the baby's gain in weight, if it does occur, is mostly a gain in weight of soft tissues, and unless this is extremely excessive, it hardly seems it could cause much dystocia.

In conclusion we might say that although occasionally pregnancies seem to go overtime, this rarely produces a serious problem and rarely warrants drastic measures. Individualization should be the keynote and then only an occasional ease will present a problem. Patients should be taught that postmaturity is rarely a problem and their anxious demands for induction of labor should be met with reassuring reasoning.

DR. P. B. RUSSELL, Memphis, Tenn.—I think one factor which is sometimes overlooked by the practitioner as well as by some of us who are specialists is the question of when quickening occurs. Sometimes this has bearing upon the medicolegal aspect of a contested paternity case. I feel the patient should return once a week from the estimated sixteenth week until the physician can hear the fetal heart tones, or fetal movements, and then a date for the confinement can be estimated at this time. Menstrual history is very unreliable in many cases. I think too many of us take the first day of the last menstrual period and then estimate the confinement from this date.

DR. RUDOLPH W. HOLMES, Charlottesville, Va.—It is a popular mot that women's first babies are often prematurely born, though the infants are of average weight and lustiness, for gossipy women will reckon from the marriage day. The literature is filled with spurious contributions on postmaturity, and I know that many practitioners have them galore, but I never have seen an authenticated case. If we imagine prolongation of pregnancy is possible, the vitally important criteria must all be indubitably evaluated—the date of the last menstruation, the date of conception, the progressive rate of uterine growth, the time of perception of fetal movements by the mother, corroborated by the physician, and the day of elicitation of the fetal heart beats (and this means an almost daily auscultation during the range when conductivity will serve its purpose). All these factors are subject to evident errors. In my opinion postmaturity is a figment of the imagination.

There is probably no phase of infection as generally misunderstood as post-abortion sepsis. An understanding of the process of inflammation as it pertains to the special problems of infected and noninfected incomplete abortion aids considerably in the intelligent handling of these cases. There is often a toxemia produced by the absorption of toxins resulting from necrosis of retained placental fragments. Any of the infecting organisms, singly or in combination, may be found in the postabortal uterus in all cases after the first 24 hours.¹⁵

Fundamentally, there are two general types of infection involved in incomplete abortion: the noninvasive and the invasive infections.¹⁶ The noninvasive infections are usually limited to the mucosal surface and are produced predominately by the saprophytic group of bacterial organisms. The pyogenic cocci constitute the group responsible for the invasive type of infection.¹⁷

The early activities of the saprophytic organisms are largely limited to necrotic tissue, and the toxemia accompanying such infections is due to the absorption of degradation products resulting from chemical changes and bacterial activity in the necrotic tissue remnants.¹⁶ The anaerobic streptococci group is made up of a large number of strains and is probably more than an occasional constituent of the normal vaginal flora.¹⁷⁻²⁰ These organisms find conditions favorable to them in the necrotic tissue of the incompletely evacuated uterus,²¹ are responsible for many of the toxic symptoms,²² and are frequently associated with the occurrence of suppurative thrombophlebitis in the pelvic veins.^{23, 24}

Invasive infections differ from the noninvasive infections principally in that the organisms involved spread by the way of tissue spaces and lymphatics instead of along the surface.^{12, 15, 16, 25} The essential feature is an invasion of the cervix beyond the so-called protective leucocytic zone. It is this type of infection that favors a poor prognosis.

The organisms found most constantly in the critical and fatal cases of infected incomplete abortion are the beta hemolytic streptococci.²⁶ Consequently, cervical or uterine cultures containing beta hemolytic streptococci have indicated that instrumental interference may aid this invasive group of organisms. This factor excluded a large group of patients from active treatment.

Lancefield and her associates²⁷⁻³⁰ by means of a precipitin reaction employing C carbohydrate antigens, isolated many varieties of beta hemolytic streptococci, of which only a relatively few strains were found to be extremely invasive in the human body. Therefore, the ability of streptococci to hemolyze blood agar media is in itself no longer a suitable criterion of invasiveness.³¹ The most invasive and consequently the variety most often associated with a poor prognosis were placed in Group A. The less invasive beta hemolytic streptococci, and thus less often associated with a poor prognosis, were placed in Groups B, C, D, E, F, G, H, and K. Hemolytic streptococci of Group A variety are very rarely, if ever, present in the bacterial flora of the female genital tract.²³ This explains why, in the past, hemolytic streptococci have been isolated from the cervix and uterine cavity in cases of genital tract sepsis; some cases were critically ill, and others scarcely so at all.³² The presence of Group A organisms, and not the entire group of beta hemolytic streptococci, in uterine cultures, should thus temporarily contraindicate active treatment in cases of infected incomplete abortion.

With the advent of the sulfonamide group of drugs and later, penicillin, it was believed that a panacea had been discovered for all infections; consequently, the active surgical management of septic abortion was believed to be unnecessary. However, with the general use of the sulfonamide drugs since

THE SURGICAL MANAGEMENT OF INCOMPLETE ABORTION*

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THE abortion problem as a whole is one of increasing importance since it is directly responsible for an alarmingly high maternal mortality rate. Of the 25,938 maternal deaths in the United States which occurred in the three-year period, 1939 through 1941, nineteen per cent were directly due to abortion.¹ During 1942 there were 7,956 maternal deaths in the United States, of which 1,384 were directly attributed to abortion. Infection was by far the leading cause of death in these reports.¹ Although during 1944 the national maternal mortality rate reached a record low of 6,369 deaths, 36 per cent were caused by puerperal infection.² Two-thirds of the deaths following abortion, both in 1943 and in 1944, were attributed to infection.²

Less tangible is the permanent damage produced in the female generative tract resulting directly or indirectly from abortion.

Management of incomplete noninfected or infected abortion presents one of the most difficult problems with which the obstetrician or gynecologist must deal. The treatment usually resolves itself into some modification of one of two methods—conservative or surgical. Briefly, the conservative method consists of supportive measures, complete bed rest and the administration of oxytocics in an attempt to influence the uterus to empty itself without instrumental aid.³⁻⁶ In a large and representative series of cases where conservative management was used, the average duration of symptoms before completion of the abortion was four weeks and four days.^{7, 8}

The surgical method combines all the features of conservative management and, in addition, the uterus is emptied by instrumentation, provided the patient's condition is such that she does not constitute a poor surgical and anesthetic risk. Advocates of this procedure have shown that uterine involution is more rapid, and normal menstrual rhythm is established more quickly after surgical completion of the abortion, while the period of hospitalization is much shorter.⁹⁻¹³ Patients cared for in this manner show low morbidity, and mortality rates which compare favorably with those of the more conservative management.^{9, 12}

However, this method is not without danger, since it is difficult, if not at times impossible, to distinguish between infected and noninfected incomplete abortion. Due to absorption of toxic products from necrotic retained secundines, the so-called noninfected case may exhibit many clinical features resembling the infected case.¹⁴ The uncertainty involved in choosing the proper cases for surgical management constitutes a weak feature.

*Read before the Central Association of Obstetricians and Gynecologists at Louisville, Ky., on Oct. 23, 1947.

were present in the uterine cavity. All of this information was usually available within eighteen to twenty-four hours after the culture was taken. In 95 cases thus examined, three were found harboring Group A hemolytic streptococci.

During the twenty-four to thirty-six hour period of observation, an injection of one c.c. of obstetric Pituitrin intramuscularly and Ergotrate, mg. 0.2 by mouth, every four hours were administered. If the patient's oral temperature was greatly elevated (100.2° F. or more) after admission, one of the sulfonamide group of drugs in adequate doses was given orally. Later in the series, penicillin was used either alone, or in combination with sulfadiazine. Absence of adnexal involvement or pelvic abscess formation was believed to be due to the liberal use of chemotherapy and particularly after penicillin was added to the treatment regime.

At the end of twenty-four to thirty-six hours, the cervical culture and the Laneefield precipitin reaction results were reported. In the absence of Group A hemolytic streptococci in the uterine cavity and with the abortion again judged to be incomplete as evidenced by continued vaginal bleeding and lower abdominal cramping, the patient was then prepared for a curettement under anesthesia.

Prior to actual curettage, the depth of the uterine cavity was carefully measured and then the cavity systematically curetted with a large curette. It was felt that perforation would be less likely to occur when a large curette was employed.

A series of 95 cases of incomplete abortion was treated by the so-called radical method. Patients in this group were not dismissed from the hospital until the oral temperature was normal for 24 hours and other signs of toxemia were absent for the same period. The sooner the cases were treated in this manner, the shorter the period of morbidity. In this group of cases the average number of postoperative hospital days was 4.0; the number of days of morbidity averaged 3.1, while there were no deaths.

The following table is included in an attempt to compare the method reported herein with cases cared for by more conservative measures, where bacteriologic procedures were not employed to aid in the selection of cases. (Table I.)

TABLE I. TREATMENT RESULTS COMPARED

| | SURGICAL | SURGICAL ¹ (J. D. H.) | CONSERVATIVE ² (J. S. H.) | CONSERVATIVE ¹ (J. D. H.) |
|------------------------------|----------|-------------------------------------|---|---|
| Number of cases | 95 | 55 | 100 | 34 |
| Average days in hospital | 4.9 | 5.1 | 11.3 | 12.3 |
| Days of morbidity | 3.1 | 3.8 | 7.8 | 9.1 |
| Cases subsequently curetted | 3 | 0 | 24 | 18 |
| Cases with group A organisms | 3 | Not determined | Not determined | Not determined |
| Mortality | 0 | 1.8% (1) | 3% (3) | **2.1% (1) |

¹Jefferson Davis Hospital.

²John Sealy Hospital

*infection.

**hemorrhage.

The three patients whose cervical cultures contained Group A beta hemolytic streptococci were treated by small repeated transfusions, oxytocics, and adequate sulfonamide and/or penicillin until the intranterine cultures failed to reveal the presence of Group A organisms and the clinical picture was not

1937 and, more recently, penicillin, the national mortality percentages resulting from postabortal infection have been reduced little.^{1, 2, 33}

Sulfonamide inhibitors have been demonstrated in necrotic tissue.³⁴ The sulfonamide inhibitors, the most important of which is para-aminobenzoic acid,³⁵⁻³⁷ are bound up in the tissue proteins and are not capable of inhibiting the action of the sulfonamides until released through the necrotic breakdown of proteins^{34, 38}; hence, the relative ineffectiveness of the sulfonamide drugs in combating the saprophytic type of infection. Furthermore, the anaerobic streptococci are very sulfonamide³⁹ and penicillin resistant.⁴⁰

Recent clinical reports⁴¹ indicate that penicillin and sulfonamides, although given early and in adequate amounts, were without effect in many cases of septic abortion. Many authoritative data indicate that there are enzymelike penicillin inhibitors.^{40, 42} Many of the pathogenic organisms do not produce enzymelike penicillin inhibitors, but are found in combination with secondarily invading organisms which do produce the inhibiting factor, thus neutralizing the bacteriostatic activity of the penicillin against the primary invading penicillin-susceptible organisms.^{40, 43}

The production of the penicillin inhibitors is probably not the only factor determining bacterial resistance to penicillin. Accumulations of pus, dead tissue, and fibrin definitely offer mechanical interference to the diffusion and efficiency of penicillin.⁴⁴

Obviously, removal of the necrotic intrauterine debris is necessary to eliminate the source of sulfonamide inhibitor substances, and to remove the chemical and mechanical barriers to penicillin. In addition, removal of the necrotic material eliminates the favorable environment for the less invasive bacteria. The virulent (Group A) hemolytic streptococci tend, in their early stages, to spread rapidly through the tissues without causing necrosis in the infected area. Fortunately, in this small group, the sulfonamide drugs and antibiotics produce their most striking effects.^{39, 45, 46}

It was with this information and reasoning that the following procedure was developed.

Procedure

On admission to the hospital each case of incomplete abortion was subjected to the following:

1. Examination:
 - a. Temperature, pulse, respiration rates, blood pressure determination, and interne's physical examination.
 - b. Laboratory examination of peripheral blood.
 - c. Sterile, bimanual, pelvic examination to aid in determining whether or not the infection had extended beyond the uterus.
2. Removal of loose tissue present in the vagina or cervix with sponge forceps.
3. Culture taken from within the uterine cavity.

If, from laboratory studies and clinical impression, it was deemed necessary, a citrated blood transfusion of 350 c.c. to 500 c.c. was given and repeated when required.

Culture swabs containing material from within the cervix were streaked on blood agar plates and broth culture media were inoculated. Both were incubated and the blood agar plates observed in twelve and sixteen hours for characteristic minute colonies surrounded by a wide zone of hemolysis. The Lancefield micro-precipitin method was used to determine whether or not Group A streptococci

Discussion

DR. RUDOLPH W. HOLMES, Charlottesville, Va.—It happened to have been my fortune to have been appointed chairman of The Committee on Criminal Abortion of the Chicago Medical Society. As a result of this, I became an honorary coroner's physician and deputy coroner for some five or six years. I witnessed the autopsies on the majority of the women who actually or putatively died from the criminal assault. I firmly believe that there are as many, if not more, criminal operations performed as there are near-term babies. A woman who glibly acknowledges the fact may be believed; if she denies the origin too many times she is lacking in veracity.

As my recollection goes, at least one-quarter of the women who came to the postmortem table showed marked traumatism of the genital tract—mostly uterine perforations, though cervical and vaginal injuries were frequent. The lamentable picture is that at least one-half of these injuries were produced by overzealous, perhaps unskilled addicts in the use of the sharp curette or placental forceps. The pity of it is, that, no matter how conclusively it is revealed that the abortionist had operated, the defense lawyer will invalidate all testimony by averring the second doctor was responsible for the trauma. Recamier introduced the curette in 1802. I have asserted for years that it is a physically impossible feat completely to scrape the uterine mucosa in or out of the pregnant state: true, gross fragments of the decidua may be caught and removed, but that is all. Where are the gynecologic pathologists and clinicians that they have not heard of the *reaction zone of Braun*! This reaction is merely the inflammatory reaction which occurs in all localized infections, whether there be an abscess forming or actually in existence. What surgeon would open an abscess and then curette the wall! An infected uterus is only a self-draining abscess.

DR. P. B. RUSSELL, Memphis, Tenn.—I corroborate Dr. Holmes' remarks about the rupture of the uterus. I have seen two very good operators go completely through the fundus or some other part of the uterus while curetting.

I wish to congratulate Dr. Morse upon his report and about his remarks concerning the examination and making cultures, in particular. To me this is one of the most important things in the consideration of a criminal abortion. Most of these patients are infected when they come in and it is almost unbelievable that anyone would invade the uterine cavity without first taking a smear and/or culture from the cervical canal, and thereby try to determine the lethal organisms. Last November I read a paper, during the Southern Medical Association Meeting, in which I reported 3,379 cases of abortion. In this series there were 202 operative procedures, and 91 of these were proved not to be cases of pregnancy, based upon the report of the pathology department. Eight of the patients in this series were curetted more than once. Some may argue, if you do not curette these patients, there is the possibility of a chorionepithelioma developing at a later date. Out of a very large series investigated, there was one in the 113,238 cases with this condition and she was not a case of an abortion, but one of premature delivery. Therefore, I refute the argument it is better to curette than to risk the development of a chorionepithelioma if surgery is omitted. Too, in a patient with an endometritis and fever, one does not curette the patient, and yet, many will curette a patient with an infected abortion. I do not think it is wise to do so, routinely.

DR. ROBERT J. CROSSEN, St. Louis, Missouri.—As early as 1927 we have treated infected abortion by gentle removal of any retained secundines by means of a sponge forceps. This is followed by intrauterine douche of 1:2000 potassium permanganate. By culturing each case, the anaerobic bacilli were usually found to be the source of the infection. These patients were able to leave the hospital in five to seven days. Some years ago at Washington University we started using instillation of mercurochrome in glycerine in the vagina of all cases in labor and found that it reduced the morbidity. Recently we have been using 1 per cent neutral acriflavine in glycerine.

that of extreme sepsis. If the abortion was judged to be incomplete at this time, a eurette débridement was performed. Subsequently, all three cases were curetted.

These results indicate that, with a careful selection of cases by now-available and not too technical methods, a larger number of patients can be treated surgically for incomplete abortion, thereby appreciably reducing the mortality and morbidity rates and period of hospitalization. Furthermore, the sooner the eurettement is performed after the abortion, the shorter the period of post-operative morbidity and hospitalization.

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AMEBIC VAGINITIS*

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AMEBIC vaginitis is a rare vaginal infection first reported in the United States in 1944 by de Rivas.¹ In 1943, Bickers,² in a study of 200 cases of leucorrhea, observed that 0.5 per cent were caused by *Endameba histolytica* but did not report any cases. Baegalupo and associates³ of Argentina reviewed the literature in 1942 and described one case. Since then cases have been reported by May,⁴ Morse and Seaton,⁵ Cleland⁶ and de Rivas.¹ It is interesting to note that in 1928 Hegner⁷ reported the presence of *Endameba nana* in vaginal washings obtained by Hartman in the course of some experiments on rhesus monkeys.

It is well known that the incidence of amebic infestation in the United States is high.⁸ The incidence of amebiasis in routine stool examinations on all patients admitted to Touro Infirmary ranges from 3 per cent to 5 per cent. Despite the numerous cases of amebiasis encountered among the admissions to Touro, there has been no instance of amebic vaginitis diagnosed prior to the four cases to be reported in this paper.

Although only ten cases of amebic vaginitis were found in a review of the literature from 1916 through 1946, within a period of nine months in 1946 we have treated four patients with this condition. The first patient was seen in April, 1946; this case was reported by one of us (B. B. W.) at a meeting of the Obstetric and Gynecologic Residents of Touro Infirmary. The second patient was admitted in June, the third in August, and the fourth in December, 1946. Although thorough examinations for parasites have been made since, no further instance of amebic vaginitis has been encountered.

Report of Cases

CASE 1.—Mrs. C. E., aged 29 years, was seen in April, 1946, complaining of irregular bloody vaginal discharge first noticed in December, 1945. It was unaccompanied by pain or pruritus and did not have a particularly foul odor. It occurred more or less continuously throughout the month with no relation to the menstrual period. The patient consulted her local physician in January, 1946, because of dyspareunia and was given several types of soothing douche powders which she used for the next two months with no appreciable improvement. There was no history of intestinal disorders.

Pelvic examination revealed a serosanguineous discharge. The cervix had an irregular erosion, eccentrically placed, occupying an area of 2 cm. by 3 cm. between five and nine o'clock on the cervix. The uterus was slightly enlarged, exquisitely tender and freely movable.

*Read before the meeting of the Central Association of Obstetricians and Gynecologists, Louisville, Ky., Oct. 25, 1947.

DR. CHARLES GALLOWAY, Evanston, Ill.—I published a paper not long ago based on 1,114 cases of abortion admitted to the Evanston Hospital. This included 643 incomplete abortions and 605 of those were curetted. We had one death due to hemorrhage but this patient was practically exsanguinated by the time she reached the hospital.

The best way to treat such a patient is to empty the uterus early, get the cervix closed down and the case terminated so that she may again resume her normal life. One of the best ways to infect your patient is to allow the uterus to remain open and all the vaginal bacteria to enter this very fertile field.

DR. MORSE (Closing).—The three cases that showed group A hemolytic streptococci were admitted criminal abortions.

All agree that the uterus should be curetted if there is profuse bleeding. About 15 per cent of all incomplete abortions are curetted because of hemorrhage in the presence of fever. Why is there such a change in attitude when hemorrhage is not a prominent factor?

We are familiar with the late sequelae of incomplete abortion: the menstrual rhythm is often disturbed, and many of these women subsequently become sterile. Many of the late and remote complications can be prevented if the uterus is completely emptied early.

I hope that this paper has stimulated a renewed interest in the whole problem of abortion. The statistics indicate that something must be done. The 1945 statistics reveal that the abortion mortality has changed little when compared to the 1944 rate.

Examination revealed a cystocele, a rectocele and a copious amount of bloody vaginal discharge. The vagina, when cleansed, showed pronounced senile vaginitis and was rather friable. On the cervix there was a continuous rim of erosion from about two o'clock to nine o'clock, placed at the outer periphery and about 1 cm. wide. This was granular and bled easily. The uterus was about two and a half times the normal size and contained multiple fibroids. No adnexal masses were found. Cervical biopsy revealed no evidence of carcinoma. A Papanicolaou smear also disclosed no evidence of malignant cells. Approximately a week later the patient again had a large amount of bloody vaginal discharge. Routine vaginal smears had not been previously obtained because the bleeding was attributed to the cervical lesion and the senile vaginitis and cervical carcinoma rather than vaginitis was suspected. Careful smears were then made and the trophozoite form of *E. histolytica* was demonstrated. Although the patient had given no history of intestinal irregularities, when questioned more carefully at this time, she admitted that she had had an attack of alternating diarrhea and constipation approximately a year and a half before and that she had spent about six months at that time in Central America. She had received no treatment for this intestinal disorder and she stated that after her return to the United States it had cleared up. Stool examination revealed the presence of *E. histolytica*. Treatment consisted of Vioform powder insufflation into the vagina, cleansing douches, and the systemic administration of Diodoquin and emetine. The vaginal discharge disappeared in approximately ten days. The cervix was clear when the patient was examined about a month later.

When the results of both the stool and vaginal examinations were repeatedly negative for *E. histolytica*, the patient was given some estrogenic suppositories to relieve the senile vaginitis and reported about four weeks later that she was having no symptoms. In June, 1947, after a careful examination revealed no ameba in the stool and vagina, a hysterectomy and plastic repair were performed with an uneventful convalescence.

Discussion

The following significant observations have been made almost constantly on these patients. Their complaint is usually of a serosanguineous or frankly bloody vaginal discharge, not associated with pruritus. There is a peculiar ulcerated lesion of the vagina and frequently of the cervix. The cervix is involved in approximately 70 per cent of the reported cases. In those cases which have been reported the cervical lesion is usually eccentrically placed and away from the external cervical os. There is a relatively shallow, granular, not uncommonly purulent area, which is usually extremely friable. The uterus is often enlarged, soft, engorged, and tender. In one of the cases in the literature,⁹ the diagnosis was made at autopsy and there was considerable involvement of the uterus. It is possible that many or all the cases in which the uterus is enlarged, soft, and tender have similar uterine involvement. Uterine aspiration was not done in any of the reported cases. The cervix is usually enlarged, engorged, soft, and extremely tender on palpation. These lesions are friable and bleed readily and persistently. It would be easy to confuse them with any of the granulomatous lesions, particularly carcinoma or infection from *Hemophilus* of *Ducrey*. In most of the reported cases,³⁻⁵ biopsy or scrapings were obtained at some time in an attempt to determine the causative factor. The trophozoite form of *E. histolytica* can be readily identified in a wet vaginal smear⁵ and most of the reported cases, as well as all of ours, have been associated with amebic infestation of the intestines.

The vagina appeared to be slightly eroded in several places. Examination of the vaginal discharge, both by dry and hanging drop smears, disclosed the active form of *E. histolytica*. The presence of amebas was discovered in the stool. Treatment consisted of a course of Diodoquin and emetine and vaginal insufflation of Vioform powder once daily for two weeks. The local lesion cleared up rapidly with the use of Vioform powder and cleansing douches.

CASE 2.—Mrs. L. P., aged 35 years, was admitted to Touro Infirmary in June, 1946, because of irregular vaginal bleeding which began about October, 1945, but was evidently not severe enough to cause the patient to seek medical advice until March, 1946. At this time the discharge became progressively worse and there was definite increase in vaginal tenderness until the patient could hardly tolerate speculum examination of the vagina. The discharge was a bloody, mucous, granular type which did not cause pruritus. The patient had passed blood in the stool on one occasion.

Pelvic examination revealed a bloody vaginal discharge. There was a peculiar type of erosion well away from the external os of the cervix on the right side; this was cauterized at the time of the first examination. The uterus was enlarged, pulled to the right side and thought to contain a fibroid.

Two weeks later the patient still had a bloody vaginal discharge. The cervical lesion showed no improvement and was at this time painted with a 50 per cent solution of silver nitrate. Various types of local treatment were instituted for the next two months during which time an organism consistent with *Hemophilus of Ducrey* was isolated from the vaginal discharge. The patient was then given a twenty-one-day course of sulfadiazine therapy with no results.

On June 13, 1946, the patient was admitted to the hospital for streptomycin therapy. Four days after admission a stool specimen was reported positive for *E. histolytica*. The vaginal discharge contained numerous trophozoites of *E. histolytica*. The streptomycin was discontinued and the patient was discharged from the hospital and given a 5 per cent solution of ehinofon to instill into the vagina twice daily. She was also given a course of Diodoquin and emetine. Within five days the local irritation and bloody discharge had improved remarkably. The patient, seen a month later, was completely cured. She had no vaginal tenderness, no discharge, and no areas of ulceration.

CASE 3.—Miss R. E. C., aged 21 years, presented herself in August, 1946, with the chief complaints of pruritus and "menstruating for three months."

The patient gave no history of any intestinal disorder. She had begun to menstruate at the age of 15 and menses were regular, occurring every 29 days. Even during the past three months, despite the fact that "she menstruated every day" she also had regular bleeding periods at the time the normal menses were to be expected. On examination, a bloody vaginal discharge was observed. The vagina appeared to have one or two small granular areas from which there was slight oozing. The cervix had an eccentrically placed erosion about 0.5 cm. in diameter, centering around nine o'clock and a smaller lesion at four o'clock. A smear was made of the discharge and the trophozoite form of *E. histolytica* was found. The patient received treatment similar to the previous cases and the infection subsided within three weeks; she has had no recurrences. Repeated stool examinations over a period of several months failed to demonstrate the cysts or trophozoites of *E. histolytica*. In January, 1947, the patient had a sudden attack of severe bloody diarrhea and the trophozoite form of *E. histolytica* was demonstrated in the stools. She was treated for intestinal amebiasis, and, at that time, careful examination of the vagina and cervix revealed no recurrence of vaginal and cervical infections.

CASE 4.—Mrs. E. C. P., aged 46 years, entered Touro Infirmary in December, 1946, because of a bloody vaginal discharge. At the age of 42, radium castration for fibroids was done elsewhere. She did not have pruritus, and there was no odor to the discharge. What concerned her was that she "was starting to menstruate again" after she had been assured that the radium given her would make this impossible.

Original Communications

TREATMENT OF TRICHOMONAS VAGINALIS WITH TYROTHRICIN*

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SINCE its first description clinically, the treatment of trichomonas vaginitis has been controversial. There have been a multiplicity of methods reported in the literature, this alone being *prima facie* evidence that none so far described have proved to be outstanding.

The patients for this study were observed in the Obstetrical Clinics of the Charity Hospital of Louisiana at New Orleans. Routine vaginal smears for *Trichomonas vaginalis* were made in 1,197 patients. The results of this study are shown in Table I.

It was interesting to note that of sixty patients having trichomonas vaginalis who were carefully questioned regarding symptoms, 45, or 75 per cent, gave a positive answer. These symptoms varied from a moderate discharge with little pruritus to a heavy one with marked itching and burning.

Treatment was carried out exclusively by the patient herself. She was instructed not to take douches during the intervals of treatment. She also was advised not to have intercourse; this, however, was difficult to control and was most probably not followed very well. There were two main objectives in this study. The first was to determine the value of tyrothricin in treating trichomonas vaginitis. The second objective was to determine the value of treatment by self-medication alone.

Tyrothricin is an alcohol-soluble, water-insoluble, extract of *Bacillus brevis*. It was first isolated and described by Dubos. It was used in this study in the form of suppositories having the following composition:

V-86 contains a water-soluble base, from which the suppositories were made, plus 5 mg. of tyrothricin per suppository. Its pH is 5.3.

V-82 and V-24 are similar to V-86 in that they are a combination of the water-soluble base but in addition contain proper amounts of lactic, citric, and boric acids. They contain no tyrothricin. The pH of V-82 is 1.5 and that of V-24 is 2.8.

V-32 and V-23A contain the water-soluble base with lactic and boric acids and, in addition, 5 mg. of tyrothricin. V-32 has a pH of 2.05 and V-23A a pH of 2.65.

TABLE I. INCIDENCE OF TRICHOMONAS VAGINALIS

| | WHITE | COLORED | TOTAL |
|-------------------|-------|---------|-------|
| Total examined | 255 | 942 | 1197 |
| Positive | 40 | 281 | 321 |
| Per cent positive | 15.7 | 29.8 | 26.8 |

*The Tyrothricin used in this study and funds for the survey were supplied by Sharp & Dohme, Inc., Philadelphia, Pa.

Treatment is still relatively empiric since so few cases have been reported; a variety of methods of treatment has been used. The local lesion will probably clear up spontaneously if the patient is given systemic therapy for amebic infection. However, the cases reported in this paper have responded to insufflation of the vagina with amebacidal agents, amebacidal douches, or both, combined with systemic therapy for the intestinal amebiasis.

Summary

1. Four cases of amebic vaginitis and cervicitis are reported.
2. These cases are characterized by bloody vaginal discharge without pruritus and the presence of a granular lesion in the vagina or eccentrically placed on the cervix.
3. The trophozoite form of *E. histolytica* can be demonstrated in the vaginal secretion and usually also in the stool.
4. These cases respond well to the usual amebacidal agents.
5. It is possible that cases of amebic vaginitis are overlooked or confused with other vaginal lesions.

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Discussion

DR. LAMAN GRAY, Louisville, Ky.—It is exceedingly interesting to have one of the first reports of amebic vaginitis before this Society. We have known amebiasis largely as a disease of the gastro-intestinal tract and liver, estimated by some to involve 1 to 10 per cent of the population at large. Also, there have been reports of lesions of the skin, simulating luetic ulcers. Some forms of arthritis have been attributed to amebiasis. It is most logical that the infection should occur in the vagina, because of its close proximity to the rectum.

Amebiasis of the rectum is said to be characterized by deeply punched-out ulcers with overhanging edges, the base being covered with thick, yellow exudate. The mucous membrane is said to bleed quite easily from trauma. These surface findings do not represent the true pathology, which is infiltrative inflammation, chiefly in the submucosa. We would expect similar pathology in the vagina.

Since relatively few laboratory workers are competent to identify *Endomeba histolytica*, it behooves each of us to study carefully the characteristics of this organism in order that we may identify it in our routine fresh preparations of the vagina.

Summary and Conclusions

Tyrothricin in the form of an acid suppository was used in the treatment of a group of patients having trichomonas vaginitis. A similar group was treated with an acid suppository that did not contain tyrothricin.

The results indicate that the use of tyrothricin in the treatment of trichomonas vaginitis is unsuccessful. This antibiotic, in suppository form, was not as effective as most common methods now in use.

In order to determine the change in the vaginal pH that would take place in the presence of the acid suppository, five patients having no vaginal infection were tested with this suppository. The pH of this suppository was 1.5. The results of this test are shown in Table II.

TABLE II

| VAGINAL pH BEFORE TREATMENT | 5 HOURS LATER | 11 HOURS LATER | 24 HOURS LATER |
|-----------------------------|---------------|----------------|----------------|
| 7 | 3 | 4.5 | 6 |
| 7 | 5 | 5 | 6 |
| 5 | 2 | 3-4 | 5-6 |
| 6 | 4 | 4 | 5 |
| 7 | 4 | 4 | 5-6 |

By this test it was apparent that the acid suppository did considerably lower the vaginal pH for about twelve hours. At the end of twelve hours the pH had returned almost to the same as before the insertion of the suppository. This degree of change, however, should be sufficient to produce any results that might take place from increased acidity.

A total of fifty-six patients were treated with one of the three suppositories. There were eleven white and forty-five colored patients. The results of treat-

TABLE III

| NUMBER TREATED | DURATION OF TREATMENT | DRUG USED | IMPROVED | CURED | FAILED | DID NOT RETURN |
|----------------|-----------------------|------------------------|----------|-------|--------|----------------|
| 23 | 2 to 10 wk. | Acid tyrothricin V-32 | 3 | 3 | 5 | 12 |
| 8 | 2 to 10 wk. | Acid tyrothricin V-23A | 2 | 5 | 1 | 0 |
| 15 | 2 to 10 wk. | Acid control V-24 | 5 | 4 | 2 | 4 |
| 7 | 2 to 10 wk. | Acid control V-82 | 3 | 1 | 1 | 2 |
| 3 | 2 to 10 wk. | Bland tyrothricin V-86 | 1 | 0 | 1 | 1 |
| Total 56 | | | 14 | 13 | 10 | 19 |

ment are shown in Table III and seem to indicate similar findings with both acid tyrothricin and acid control. As a matter of fact, better results were obtained from the acid control suppository. The number of cases treated with bland tyrothricin is too small to evaluate. There were thirty-seven patients given a known duration of treatment and follow-up examination. Fourteen, or thirty-seven per cent, of these were classed as improved. This meant that during the course of treatment there were relief from symptoms and negative vaginal smears. After cessation of treatment, however, the symptoms and positive smears promptly returned.

Thirteen, or 35 per cent, of the thirty-seven known patients were stated to be cured. This meant that they remained symptom free and had negative smears for two weeks after treatment was discontinued. Positive smears after that time were considered reinfections but could also probably be considered recurrences. Ten, or 27 per cent, of the thirty-seven known cases were considered failures, symptomatically and from smear examination.

The number improved or cured does not compare favorably with results of other drugs. This perhaps may be explained by the fact that all treatments were carried out by the patients themselves. Better results could possibly have been obtained if the therapy had been continued longer.

A large number of patients complained of considerable vaginal burning and irritation from both acid tyrothricin and acid control suppositories. In some instances, it was necessary to discontinue the use of these suppositories because of the burning.

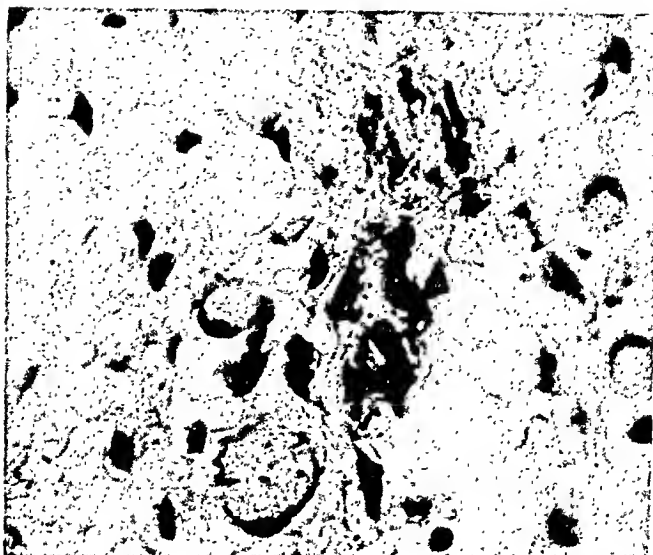


Fig. 1.—Mucoid carcinoma of the Krukenberg type with the characteristic signet-ring type of cells.



Fig. 2.—Chalky white appearance of dorsal spine is characteristic of osteoplastic metastases.

KRUKENBERG TUMOR WITH OSTEOPLASTIC METASTASES

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AMONG the numerous articles written on Krukenberg tumors no cases were found where osteoplastic metastases were noted. Following is the report of a case where massive osteoplastic metastases were seen.

H. L., a married, white multipara, 27 years old, was admitted to the Graduate Hospital in August, 1944, complaining of vaginal bleeding and a mass in the abdomen. Her medical history included a salpingo-oophorectomy for tumor of the right ovary at another hospital in August, 1943. Her postoperative convalescence was uneventful and she left the hospital on the fourteenth day. She had remained in good health for one year and had not returned for follow-up care. The pathologic report was as follows:

Specimen is a solid mass which has been previously bisected. It is 11 by 7 by 5 cm. The cut surfaces are pale yellow brown. Attached is a Fallopian tube which is hemorrhagic; it measures 3.5 by 2.5 by 2.5 cm. The microscopic picture is that of a solid tumor presenting an interesting and very unusual picture. In some regions there are solid islands of what superficially appear to be epithelial cells. The supportive structure of the ovary appears to be composed of dense, elongated cells, resembling fibroblasts. In other regions, the follicular arrangements of cells are more definite in the form of cysts, with large empty spaces lined by several rows of follicular cells.

Comment: The exact nature of this tumor cannot be determined at this time. It was the impression that the tissue resembled in part, a thecal cell tumor of the ovary and in other regions, that of folliculoma. The slides were shown to other pathologists, all of whom differed to some extent in the diagnosis, and none of whom was very definite in his opinion. One pathologist actually thought that the epithelium-like cells were truly epithelial nests and the tumor represented a Krukenberg tumor of the ovary; others felt that it represented some endocrine or developmental tumor of the ovary.

On the present admission to Graduate Hospital, University of Pennsylvania, August, 1944, the patient complained of vaginal bleeding and a mass in the abdomen. The general examination was essentially negative. The pelvic examination revealed a freely movable, firm, globular mass, the size of a large grapefruit, attached to the uterus by a pedicle. The mass was thought to be a tumor of the left ovary or a pedunculated fibroid. At operation an ovarian cyst the size of a large grapefruit, half twisted on its pedicle, was removed together with the uterus.

The ovarian tumor was 18 by 11 by 8 cm., in its greatest diameter. The capsule was thick, with a number of scarlike depressions, whitish in color, containing several cysts, the largest 3 cm., in diameter. The cut surface was pink with a background of translucent edematous tissue with rounded opaque structures. Microscopy (Dr. Case). Mucoid carcinoma of the Krukenberg type (Fig. 1).

Following the operation there were no complications except for several transfusion reactions. During her stay in the hospital an attempt was made to locate the primary growth

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1836 DELANCEY PLACE

of the Krukenberg tumor in the intestines. However, all studies of the gastrointestinal tract were negative. She was discharged in fairly good condition and resumed her household duties a few weeks later. She was treated daily by x-ray through two portals, 200 R to each portal, alternating anteriorly and posteriorly. A total of 2,000 Roentgen units (as measured in air to each portal using 190 K.V., 10 M.A., 50 cm., distance, 0.5 cm., copper, and 1 mm., aluminum filtration) was given. The lower abdominal portals measured 15 by 20 cm., the upper 10 by 15 cm. Three courses were proposed but only one course was completed before the death of the patient.

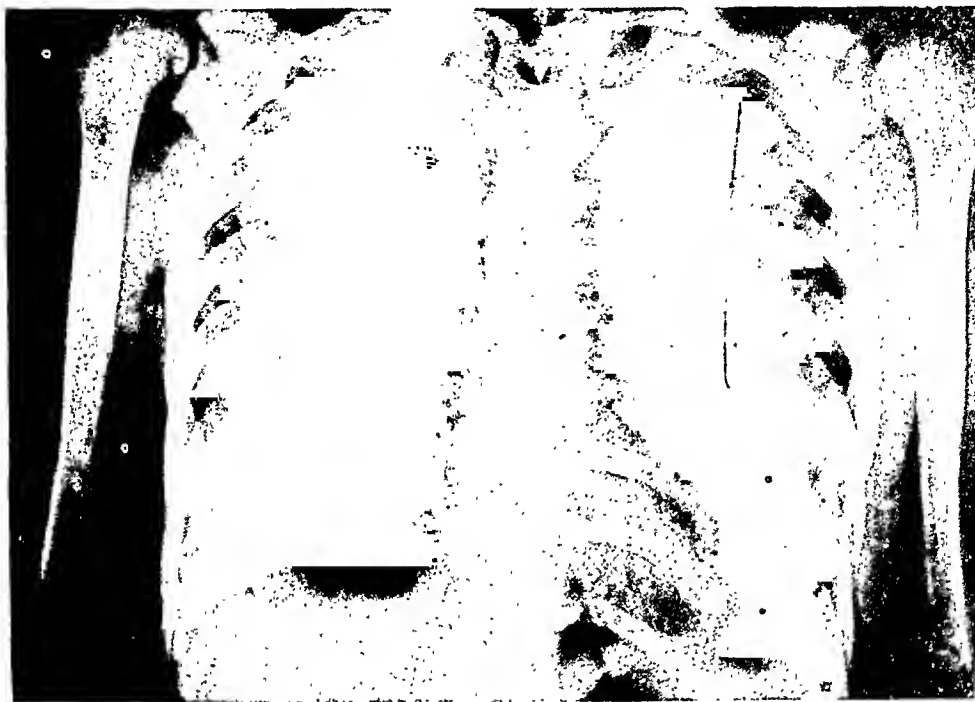


Fig. 3.—Spotty mottling involving the entire dorsal spine, upper ends of the humerus and ribs, due to osteoplastic metastases.

She enjoyed good health the following five months, gained weight, and was not offering any complaints. At the end of the fifth month she began to complain of pain in the dorso-lumbar spine and both thighs (Fig. 2).

An x-ray survey of the entire skeleton at this time showed varying degrees of osteoplasia, involving all the ribs, the clavicles, the scapulae, the upper three-fourths of both humeri, and most of the cervical vertebrae (especially the second and seventh). There was also a very slight increase in density of the pelvic bones, especially the right and left ischium. The skull and the bones distal to the elbows and knees were not involved (Fig. 3).

From here on her health began to fail rapidly. There was a progressive anorexia with loss of weight, emaciation, secondary anemia and excruciating pains in the involved bones. Patient died three months after the onset of the metastatic bone symptoms, and eight months after the second operation. Autopsy was not obtained.

Comment

In the few reported cases of ovarian carcinoma when bone metastases were seen, the bone pathology was predominantly a process of osteoclasia. In our case, however, we found an opposite picture of bone pathology, namely, osteoplasia. The cause of this unusual deviation is not known. One may consider the relationship of hormones, since it is known that estrogen may cause a deposition of calcium in the secondary trabeculae of the bone.

administered. The patient continued to vomit bloody material. Blood nonprotein nitrogen and uric acid showed a gradual rise. On August 31, the nonprotein nitrogen was 97, uric acid 8. On September 1, the nonprotein nitrogen was 146. Despite continuous intravenous fluids, oxygen, and adrenal cortical extract, the patient remained in a critical condition and expired on September 2, eight days after admission to the hospital.

Postmortem Findings.—There were superficial destruction and ulceration of the mucosa of the stomach and the lower segment of the esophagus. Microscopically, there was marked congestion of the vessels with extensive hemorrhage of the wall. Some of the vessels contained thrombi, and these showed extensive necrosis. Very little inflammatory reaction was observed. The liver showed none of the lesions considered pathognomonic of eclampsia. The heart demonstrated large hemorrhages beneath the endocardium, very pronounced along the wall of the septa, which probably accounted for clinical findings in the heart. The uterus showed severe chronic endometritis in which necrosis and masses of bacteria were noted. The kidneys and spleen demonstrated acute pyelonephritis, and acute splenic tumor was present.

CASE 2.—C. B. was a Negro woman, aged 28 years, gravida i, para 0, serology negative. Her last menstrual period was Aug. 15, 1942, and expected date of confinement was May 22, 1943.

The patient was admitted to the hospital on May 28, 1943, in mild active labor. On admission, the temperature was 99° F., pulse 80, respirations 20, blood pressure 110/70. Abdomen showed the fundus to be 26 cm. above the symphysis; position right occipitoposterior; fetal heart tones in the right lower quadrant, 140 per minute. Rectal examination revealed the cervix 3 cm. dilated, presenting part at station minus two.

The patient made very slow progress during labor. She was given adequate sedation and intravenous fluids to maintain nutrition and hydration.

Two days after admission, the patient's temperature rose to 102° F., pulse 110, respirations 30. X-ray of the chest at this time was negative. Urinalysis was also negative at this time. Rise in temperature was attributed to an intrauterine infection, and the patient was placed on sulfathiazole therapy. Sedation and fluids were maintained, and, in addition, the patient was given 500 c.c. of whole blood intravenously.

On the morning of June 1, she vomited 40 to 50 c.c. of coffee-ground material which was positive for occult blood. Labor continued to progress slowly. Fetal heart tones at this time were inaudible. At 11:30 A.M. on June 1 the patient delivered a stillborn fetus weighing 8 pounds by mid forceps from the right occipitoposterior position. Blood loss was approximately 300 c.c.

Forty-eight hours after delivery, the patient vomited a considerable amount of brownish-black material which was positive for occult blood. At the same time she began to have tarry stools. She was given 1,000 c.c. of whole blood intravenously and nasal oxygen. There were no localizing symptoms or severe pain. The abdomen was soft. She continued to vomit brownish-black material and to have tarry stools. She expired on June 6, approximately five days after delivery and nine days after admission to the hospital.

Postmortem Findings.—Pathologic examination of the gastrointestinal tract revealed no lesions grossly; however, microscopically, one site in the stomach showed necrosis with numerous bacteria in the mucosa. There were approximately 2,000 c.c. of bloody stool in the intestine. The kidneys were consistent with eclampsia. The spleen was acutely inflamed. Autopsy was not completed for the family withdrew their permission suddenly.

CASE 3.—M. D. was a white woman, aged 17 years, gravida i, para 0, serology negative. Her last menstrual period was April 15, 1944, and expected date of confinement was Jan. 26, 1945. Repeated urinalyses and blood-pressure readings were normal during the prenatal course. The patient was apparently well until the morning of Dec. 4, 1944, at which time she complained of headaches and vomiting. At 7 P.M. on the same day the patient had sudden loss of vision.

On admission, the temperature was 99° F., pulse 70, respirations 22, blood pressure 190/150. The patient was in a semistuporous condition, and there was complete loss of

MASSIVE GASTRIC HEMORRHAGE IN PREGNANCY

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FOUR cases demonstrating the unusual complication of massive hemorrhage during pregnancy at term are herein reported. Review of the literature reveals that this is not a common complication. Greely and Stubenbord,¹ in 1941, reported one case of a 31-year-old patient, gravida ii, para i, at term, who had severe gastric hemorrhage, passage of tarry stools, and shock. She delivered a stillborn male fetus, following which she had an uneventful recovery.

Preiss,² in 1907, reported a case in which hematemesis occurred in the second and third pregnancies. These two pregnancies were complicated by the occurrence of sudden severe gastrointestinal hemorrhage as evidenced by vomiting of blood, bloody stools, and shock. In both pregnancies, the hematemesis occurred two weeks before the expected date of confinement. Both pregnancies resulted in the birth of normal stillborn male infants. The onset of labor and delivery occurred spontaneously within twenty-four hours after the bleeding.

Sturrock,³ in 1913, reported one case of gastric hemorrhage occurring at the time of delivery.

Greenhill⁴ mentions the fact that large hemorrhages may occur in the lumen of the gastrointestinal tract during toxemias of pregnancy.

CASE 1.—M. B., a Negro girl, aged 14 years, gravida i, para 0, at term, was admitted on Aug. 26, 1944, with a history of having had seven generalized convulsions.

The patient was a well developed, well nourished Negro girl in a semicomatose condition. Temperature 102.8° F., pulse 100, blood pressure 180/120. Ophthalmoscopic examination revealed no retinal changes. The heart and lungs were normal. The abdomen was compatible with a term pregnancy. Extremities revealed a 1 plus edema.

The patient was placed on modified Stroganoff regime. For the next three days the blood pressure remained around 160/120. The urinary output was considerably less than the fluid intake. Repeated urinalyses showed 3 to 4 plus albumin. Nonprotein nitrogen on admission was 27, and the uric acid was 3.48. Three days after admission the patient was rational and cooperative. On August 29, the patient's temperature rose to 103° F., respirations 40, pulse 140, heart rate 160, with a definite pulse deficit present. The patient was rapidly digitalized. Electrocardiogram at this time revealed a sinus tachycardia. She was given nasal oxygen and sodium sulfathiazole intravenously.

On August 30, the fetal heart tones were not audible. At 11 A.M., the patient had an episode of projectile vomiting of approximately 1,500 c.c. of coffee-ground fluid which was positive for occult blood. Blood pressure at this time was 130/100, pulse 140, temperature 101.6° F., respirations 40. One hour later the blood pressure was 90/60. The patient was given 1,000 c.c. of whole blood intravenously. She continued to have projectile vomiting of brownish-black fluid which remained positive for occult blood.

On August 31, she went into spontaneous labor and was delivered by low forceps of a macerated, stillborn fetus weighing 8 pounds 5 ounces. Blood loss was minimal. Total duration of labor was 4 hours and 18 minutes. Intravenous fluids and whole blood were constantly

Comment

Three cases presented an eclamptic syndrome of hypertension, edema, convulsions, oliguria, and albuminuria. All four had severe projectile vomiting of blood, followed by marked decrease of blood pressure. In all, the onset of labor occurred 24 to 28 hours following the onset of projectile hematemesis. Three of the patients delivered stillborn infants, in which the fetal heart tones were not audible, following the onset of hematemesis. In one case, in which the patient survived, the infant was premature and viable.

Pathologic study of Case 1 revealed no specific source of hemorrhage in the esophagus or stomach in the form of varices. However, it was noted grossly that there were marked superficial destruction and ulceration of the mucosa of the stomach and esophagus. This may have been a source of bleeding, but it was not thought that it would have produced the amount of hematemesis noted clinically. The elevated temperature was probably due to the severe chronic endometritis in which there were necrosis and masses of bacteria in the endometrium. Together with this infection, she had acute pyelonephritis bilaterally and an acute splenic tumor. The liver showed none of the lesions considered pathognomonic of eclampsia.

This infection may have been the underlying cause of her massive hematemesis and the death of the fetus.

Case 2 was not completely autopsied, for the family withdrew their permission suddenly. The gastrointestinal tract, however, contained approximately 2,000 c.c. of bloody stool. No lesions were noted grossly, although microscopically one site in the stomach showed necrosis with numerous bacteria of the mucosa.

The kidneys demonstrated focal areas of inflammation and were consistent with eclampsia. The spleen was acutely inflamed.

Cases 3 and 4 did not come to autopsy. However, they were both eclamptic and ran a septic temperature.

The hemorrhagic tendency noted may be due to eclampsia or to infection. This hemorrhage may be similar to the intrauterine hemorrhage observed in premature separation of the placenta, and the association between the latter condition and toxemia of pregnancy has long been established. The death of the fetus may be attributed to the infection or to the severe gastrointestinal bleeding causing anemia and shock.

Summary

1. Four cases of severe gastric hemorrhage in pregnancy are presented.
2. There were three deaths and one survival.
3. Three cases presented an eclamptic syndrome of hypertension, edema, convulsions, oliguria, and albuminuria.
4. All four cases ran a septic temperature.
5. All four cases had severe projectile vomiting of blood followed by marked decrease of blood pressure.
6. In three of the four cases, the onset of labor occurred 24 to 28 hours following the onset of projectile hematemesis.
7. Three cases delivered stillborn infants, and, in one case, in which the patient survived, the infant was premature and viable.

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vision bilaterally. No hemorrhages, exudates, or vascular changes were noted in the fundi. The heart and lungs were negative. The abdomen was compatible with a thirty-six week's pregnancy. The patient was not in labor.

The patient was treated with hypertonic glucose solution, magnesium sulfate intravenously, Dilaudid and Luminal Sodium for sedation. Six hours after admission, she had a convulsion and the blood pressure was recorded as 260/140. Urine obtained by catheterization showed 4 plus albumin.

Twelve hours after admission, the patient was again catheterized and 100 c.c. of prune-juice-colored urine was obtained. This urine was examined spectroscopically and found to be methemoglobin. Blood smear at this time did not reveal any malarial parasites. Platelet count was 100,000. Red blood cell fragility test ranged from 0.48 per cent to 0.36 per cent. Spinal puncture was performed twelve hours after admission, and 100 c.c. of xanthochromic spinal fluid were removed under moderate pressure. Blood pressure following the puncture was 180/130. Hypertonic fluids and sedation were continued, and the blood pressure remained consistently elevated. Repeated urinalyses revealed 3 to 4 plus albumin, and the sediment was loaded with red blood cells.

Eighteen hours after admission, the patient's blood pressure was 140/120. At this time she had projectile vomiting of a coffee-ground material which was positive for occult blood. Blood pressure following this episode of vomiting was 140/120. She immediately started to have irregular uterine contractions, and the membranes were ruptured artificially at 2 P.M. on December 5. At 7 P.M. a stillborn fetus weighing 4 pounds 4 ounces was delivered by low forceps. Postpartum bleeding was minimal.

Despite hypertonic glucose solutions, magnesium sulfate, plasma, and whole blood the patient failed to show any satisfactory improvement. Blood pressure consistently remained elevated. Pulse was rapid and of poor quality. Urinary output continued to be minimal and consisted of dark-colored fluid. The patient's temperature gradually rose to 105° F. Vomiting of coffee-ground material continued. Blood nonprotein nitrogen showed a gradual rise, and, on December 5, the nonprotein nitrogen was 43. On December 7 and 9 the nonprotein nitrogen was 104 and 88 respectively. On December 11, the nonprotein nitrogen was 264. The patient expired on December 11, approximately eight days after admission and six days after delivery.

CASE 4.—I. L. S. was a 36-year-old Negro woman, gravida xiv, para xii, who entered the hospital on April 25, 1946, with a history of having had three convulsions. Her last menstrual period was Aug. 13, 1945, and her expected date of confinement was May 20, 1946.

The patient was an obese Negro woman in a semicomatose condition. Temperature 101° F., pulse 120, respirations 30, blood pressure 190/130. Ophthalmoscopic examination revealed marked arteriospasm with a small hemorrhage in the right retina at the upper margin of the macula. Uterus was compatible with the size of a thirty-six week's pregnancy. There was generalized edema of the lower extremities, of the hands, and of the face.

She was treated with sedation, Luminal Sodium, hypertonic glucose, magnesium sulfate, calcium chloride, and plasma transfusions. Urinalysis revealed 4 plus albumin with many fine and coarse granular casts. Nonprotein nitrogen on admission was 55 mg. The urine was bloody. On April 26, 1946, the patient had an episode of projectile vomiting of coffee-ground material which was positive for occult blood. At 10 P.M. the same day, the membranes were ruptured artificially in an effort to induce labor. She started to have uterine contractions and delivered a viable, premature male infant at 8 A.M. on April 27, 1946. Following delivery, the patient's blood pressure dropped to 150/100. She remained in a comatose condition. Temperature was 102° F., pulse 130, respirations 30. Penicillin therapy was instituted. Plasma and blood transfusions magnesium sulfate, hypertonic glucose, and nasal oxygen were continued. The edema gradually disappeared, and she began to respond. Her blood pressure appeared to be stabilized and remained at the level of 140/100. She was discharged on May 20, in good condition. Blood pressure at this time was 130/80, and the urine was negative for albumin and casts.

employed. Patients were frequently discharged on the third or fourth day, but the average hospital stay was seven and one-half days. There was one death, a patient moribund on admission, who had been ill a month. Necropsy revealed a generalized *Cl. welchii* septicemia. The authors believe the results superior to the conservative method of treatment.

R. G. DOUGLAS.

Cesarean Section

Smith, William P.: Cesarean Section Seven Years After Hemi-Hysterectomy in a Bicornuate Uterus, *Am. J. Surg.* 74: 856, 1947.

The author briefly reviews congenital uterine malformations and then reports an interesting case of pregnancy following an operation for a bicornuate uterus. This patient was first seen at the age of 13 years after a diagnosis of rectal abscess had been made and a rectal incision made for its drainage. The abnormality proved to be that of a bicornuate uterus with one cervix connected with the right uterine cavity, the left cavity having no cervical canal; this left cavity had developed a hematometra with the child's menarche, and this was infected with the attempt at drainage through the rectum. A laparotomy was finally performed and the left half of the uterus removed.

The patient menstruated normally thereafter, and eventually married and became pregnant at the age of 20 years. Pregnancy proceeded uneventfully and the patient was delivered by cesarean section in her eighth month. The operator noted the left uterine wall to be thinned; the threat of possible rupture in labor is emphasized.

S. B. GUSBERG.

Heffernan, Roy J., and Sullivan, Charles Leavitt: Which Type Cesarean Section? *New England J. Med.* 238: 241, 1948.

This concise informative article on the value of the different types of cesarean section is based on the long experience of the authors and their extensive collection of sound statistical information.

Beginning with the classical cesarean section, since it is the oldest type, they found 15,030 patients who had been subjected to the classical operation. The mortality was 3.87 per cent, a most significant finding.

Notwithstanding better obstetric management, improved operative technique, replacement of blood, and chemotherapy and the antibiotics, peritonitis still occurs. The authors agree that this type of abdominal delivery has so many disadvantages that it should be used only when better methods are not applicable or when the uterus is to be removed.

In a series of 14,776 low flap or low-cervical cesarean sections, the mortality was 1.52 per cent. It is, therefore, apparent that the lower segment operation is over twice as safe as the classic operation.

The authors find the lower-segment operation a very satisfactory type of abdominal delivery in uncomplicated, clean cases, but not without danger in the potentially infected case, since it does not ensure protection against peritonitis from the spill or seepage of infected uterine contents.

They point out that the lower-segment cesarean is usually a safe and satisfactory procedure when done electively, when the patients have been in labor ten hours or less, with intact membranes, or where there has been no vaginal examination, or membranes ruptured longer than six hours.

For the potentially infected parturient, Heffernan and Leavitt perform the extraperitoneal cesarean section. Their indications for this procedure are: 1. the slightest suspicion of infection, 2. ruptured membranes for a period of eight hours, 3. labor of more than six hours' duration, and 4. cases where repeated rectal or vaginal examinations have been made.

In a series of 1089 modern extraperitoneal cesarean sections the mortality was 0.82 per cent. Four patients succumbed to sepsis and two to postoperative hemorrhage.

Department of Reviews and Abstracts

Selected Abstracts

Abortions

Licciardello, A. T., and Stanbury, J. B.: Acute Hemolytic Anemia From Quinine Used as an Abortifacient, *New England J. Med.* 238: 120, 1948.

Acute hemolytic anemia following the administration of quinine has rarely been observed except in the presence of malaria. However, Terplan and Javert found eight cases in the literature. All these patients were women who had taken or been given quinine as an abortifacient. All died.

The authors report a patient who, two weeks after admission to the hospital, admitted having taken nine large capsules containing a white powder to interrupt a suspected pregnancy. The white powder proved to be quinine, as 1.3 mg. of quinine per liter were recovered from the urine on the day of her admission to the hospital.

Her hospital course was stormy, characterized by elevated temperature, jaundice, hemoglobinuria, albuminuria, nitrogen retention and a severe anemia, the result of hemolysis of her red blood cells. The patient recovered and was discharged on her 44th hospital day.

This report serves to call attention to the fact that quinine is an occasional cause of severe hemolytic anemia associated with jaundice and hemoglobinuria and to emphasize the danger of quinine as an abortifacient.

JAMES P. MARR.

Fouracre-Barns, H. H.: Therapeutic Abortion by Means of Soft-Soap Pastes, *Lancet*, p. 825, Dec. 6, 1947.

The author slowly injects 15 to 20 c.c. of a warm soft-soap paste into the cervix, and, in 80 per cent of 71 pregnant women so treated, abortion occurred about 24 to 48 hours later. Four patients bled excessively and seven were morbid. There were no deaths.

The article recommends this method for interrupting pregnancy in cardiac and pulmonary diseases, wherein general anesthesia is hazardous.

IRVING L. FRANK.

Corston, J. McD., and Stallworthy, John: The Treatment of Inevitable, Incomplete, and Septic Abortion, *Brit. M. J.*, p. 89, July 19, 1947.

Management of incomplete abortion by conservative measures versus prompt surgical evacuation of the uterus is discussed. The authors favor the latter method, and describe the details as applied to 600 patients admitted to the Radcliffe Infirmary with a diagnosis of incomplete or inevitable abortion. The procedure followed is to take the patient to the operating room where she is anesthetized with thiopentone and the vulva and vagina swabbed with 1:1000 flavine solution. The patient is then examined and 0.5 mg. of ergometrine is injected into the cleaned cervix. If necessary, the cervix is dilated. Retained products are removed by sponge forceps and a blunt flushing curette. The uterus is then packed with a 2 inch gauze pack which is removed six hours later. Forty-two of the total cases were infected on admission. In these cases, sulfonamide therapy was started prior to the operative procedure and the pack was impregnated with sulfathiazole powder. Seventy-one blood transfusions were

The collected results of Rh-negative transfusion in the treatment of erythroblastosis have not sustained early enthusiasm. The procedure of exsanguino-transfusion, which had been suggested in 1932 for this condition by Diamond, Blackfan and Baty, has therefore been called into use. Wallerstein, in a pioneer report on 9 cases thus treated, has given evidence adequate to show that the procedure is superior to the simple transfusion of Rh negative blood. It is emphasized that substitution transfusion should be used in the preicteric period soon after birth, before damage to the brain and liver has advanced too far. IRVING L. FRANK.

Wallerstein, H.: Substitution Transfusion: A New Treatment for Severe Erythroblastosis Fetalis, *Am. J. Dis. Child.* 19: 73, 1947. (From a long abstract in *International Medical Digest* 50: 235 1947.)

The outlook in erythroblastosis fetalis has been somewhat improved by premature induction of labor, and by repeated transfusions of Rh-negative blood. Some babies, however, have succumbed with deepening jaundice, despite these transfusions. Further treatment should be designed to remove the products of hemolysis, and to prevent their formation by the removal of the Rh-positive erythrocytes before they can be destroyed in large numbers by the maternal antibody.

Subtotal replacement of the infant's circulating blood may be carried out by removing 50 c.c. portions of blood (by syringe from the superior longitudinal sinus), in alternation with 50 c.c. blood infusions (which are added to a continuous saline or plasma infusion in an arm vein): Through five such exchanges only 80 c.c. remains of the original 250 c.c. blood volume. A supplemental 100 c.c. of Rh-negative blood is given, which further reduces the original Rh-positive blood to 25 per cent of the starting volume. Continuous simultaneous exsanguination-transfusion may be carried out by permitting the cannulized radial artery to bleed, and regulating the blood infusion to match the bleeding rate. After a 250 c.c. replacement, only 36.7 per cent of the original blood remains.

When used after toxic manifestations have become pronounced the benefits of this procedure are minimized. Substitution transfusion is recommended chiefly as a prophylactic measure, and if used in the subicteric period immediately after birth, it prevents damage to the liver and brain. The history of erythroblastosis in a previous infant is emphasized as the important indication for prophylactic treatment. At the time of delivery, icteric amniotic fluid, large pale placenta, or erythroblastosis of the cord blood may suggest the preicteric phase and indicate early treatment. If, on the basis of these criteria, one anticipates that severe erythroblastosis may develop, it is best that substitution transfusion be given as soon as possible after birth. IRVING L. FRANK.

Wallerstein, Harry: Substitution Transfusion: A New Treatment for Severe Erythroblastosis Fetalis, *Am. J. Dis. Child.* 73: 19, 1947.

Erythroblastosis fetalis has long been recognized as a hemolytic disease of unknown origin with varying degrees of anemia and hepatic damage.

Therapy, even before the recent elucidation of the pathogenesis, was directed at correction of the anemia by repeated transfusions.

Since 1941 refinement in the treatment of erythroblastosis, based on the role of the Rh factor, have resulted in a decidedly improved prognosis.

The significance of hepatic damage induced by excessive red blood cell hemolysis and the accompanying reactive liver erythropoiesis made it evident that a new and radically different approach to the therapy of erythroblastosis was required.

The procedure consists of the actual withdrawal of the infant's Rh-positive cells and their replacement with innocuous Rh-negative erythrocytes. In order to avoid subjecting the child to the dangers of shock from exsanguination, the withdrawal and replacement are carried out simultaneously. The differential typing of cells removed at the beginning and at the end of the exchange confirms the fact that only 20 to 25 per cent of the original Rh-positive erythrocytes remained.

A technique is given and seven cases are reported.

JAMES P. MARR.

The authors report 72 extraperitoneal cesareans from their own experience. There was no fetal or maternal mortality. With excellent illustrations, they describe in detail their technique in performing this lifesaving operation.

Both authors reject cesarean hysterectomy for infection, revealing a maternal mortality of 14.2 per cent in 119 such operations. Their rejection is due also to the loss of the reproductive organ, which the operation entails, besides the shock and additional blood loss at the time of the operation. They reserve a place for cesarean hysterectomy, however, for those patients with multiple fibroids, atonic uterus, or other pathologic conditions of the uterus.

They report the experience of Baird, a maternal mortality of 7 per cent in 147 cases necessitating craniotomy, only to condemn craniotomy on the living child.

They conclude that the modern extraperitoneal cesarean section is not only the safest method for the infected or potentially infected parturient patient but also may be used to advantage for less imperative indications.

JAMES P. MARR.

Gray, T. Cecil: d-Tubocurarine in Cesarean Section, *Brit. M. J.* 1: 444, April 5, 1947.

The technique employed in anesthetization of 30 patients for cesarean section is described. 0.65 mg. of atropine is given one hour before operation. d-Tubocurarine (Tubarine, Burroughs Wellcome & Co.), 15 mg. is injected, with the patient on the table, followed by 0.3 Gm. Kemithal (cyclohexenyl-allyl-thiobarbiturate) in 5 per cent solution. (Technique not stated.) "Closed circuit" cyclopropane anesthesia is then commenced at once. The operation may be started as soon as the patient fails to respond to painful stimuli. An airway is not employed because of the light anesthesia. Vomiting is avoided by this means. No evidence of curarization was evident in the babies. The uterus contracted so firmly that the use of Pituitrin was abandoned. Because of the light anesthesia the patient usually "awakens" as the dressings are applied. Postoperative complications were minimal.

The author believes the results warrant the exploration of the possibilities of this form of anesthesia by others.

R. G. DOUGLAS.

Newborn

Wiener, A. S., Wexler, I. B., and Grundfast, T. H.: Therapy of Erythroblastosis Fetalis With Exchange Transfusion, *Bull. New York Acad. Med.* 23: 207, 1947.

In 1925 Hart successfully treated a case of icterus gravis by exchange transfusion. These authors first employed exchange transfusions in 1944 on an infant with mongolian idiocy. In this, and in a subsequently treated case of icterus gravis, coagulation interfered seriously with withdrawal of blood. In 1946, following Wallerstein's encouraging results in erythroblastosis, the authors again used exchange transfusions, after heparinization of the infant's blood. Three 200 unit doses of heparin are used during the exchange. In seventeen cases known to the authors, heparin has proved innocuous, and does not magnify possible silent intracranial hemorrhages (which Wallerstein considered a dangerous possibility).

The infusion enters the saphenous vein, while blood is draining from the radial artery. The total exchange is twice the total blood volume (or, about 500 c.c.), which results in 90 per cent substitution. Success depends on the fate of the remaining Rh-positive cells. If lysis occurs, no harm results. If clumping occurs, the circulation is obstructed, and the procedure has been a failure. To avoid clumping (intravascular conglutination), the authors suggest that the conglutinin content of the donor blood be reduced by replacing one-half the plasma by saline. Polycythemia from overtransfusion should be avoided.

IRVING L. FRANK.

Exsanguination-Transfusion in Erythroblastosis Fetalis, *Internat. Med. Digest* 50: 246, 1947.

Exsanguination-transfusion, or the exchange of good blood for bad, was first proposed in 1921. At that time Robertson reported its use in the treatment of severe burns in infants and children, and later in treatment of erysipelas, septic scarlatina and acute intestinal intoxication. Subsequently others used it in the treatment of poisoning by resorcin, mercuric chloride and phenol, and in treatment of typhoid fever.

Correspondence

Death From Placenta Previa

To the Editor:

I have read with interest the case reported by Dr. Brody under Correspondence in the February, 1948, issue of the JOURNAL, purporting to be a death due to placenta previa in which there was neither intrauterine nor intracervical manipulation.

A copy of Dorland's Medical Dictionary has been sent to Dr. Brody for his effort and thoughtfulness in trying to find a case of placenta previa, uncomplicated by accreta, as mentioned in my paper, in which there had been neither intracervical nor intrauterine manipulation, but which, nevertheless, terminated in death. Obviously, sudden or immediate exitus in placenta previa has only one cause—such loss of blood as is incompatible with life. In many cases of sudden death in obstetrics, autopsy findings are necessary to determine whether the death was due to hemorrhage, or partially to hemorrhage, with shock being the major element.

Unfortunately, for two reasons, I cannot use this case to start my series: (1) There is no definite proof that the case was one of placenta previa, and (2) there is no proof that the patient died from hemorrhage. These points will be discussed.

Dr. Brody states: "At midnight she began to feel abdominal pains and discomfort, which became rapidly worse. She was rushed to the hospital." On admission to the hospital she was "cyanotic with labored breathing." Examination "revealed a full-term uterus which was hard and tender. Fifteen minutes later, while the patient was being shaved, she had a profuse hemorrhage from the vagina; . . . one-half hour after . . . she was in complete shock, restless, tossing in bed, and gasping for breath. Plasma was administered . . . the patient expired twenty minutes later." It would be most unfair to assume that the plasma had anything to do with the exitus of this shocked but restless and tossing patient who expired twenty minutes after the intravenous therapy.

The autopsy findings showed "congestion and edema of the lungs," which are common in shock, "a full-term fetus in utero, and a placenta lying in the lower pole[?] of the uterine cavity." There was no reported careful examination, such as microscopic sections to show the real attachment site of the placenta; nor whether the abdominal viscera were pale or edematous with subcapsular petechial hemorrhages.

In contradistinction to the foregoing facts reported for Dr. Brody's case, and leaving your readers to draw their own conclusions, it might be in order to state that the amount of bleeding at any given period in labor, or before labor in a case of placenta previa, depends entirely on the cervical effacement and dilatation with its consequent placental separation; placenta previa is unaccompanied by pain, uterine tenderness, or hardness; and, if the loss of blood were to become lethal, autopsy findings would be that of what is commonly designated "bled white," i.e., none of the viscera, including the lungs, would show any evidence of edema, but would be pale in color. The labored breathing indicated that pulmonary edema was present prior to death. No attempt was made to explain the hyperpyrexia.

It seems to me that Dr. Brody was unfortunate in encountering a fatal case of premature separation of the placenta regardless of the latter's site of attachment. The separation was sudden and massive and gave rise to the clinical symptoms as described by him and followed rapidly by death. The autopsy finding of edema of the lungs tends to confirm the opinion that death was due to shock and not to loss of blood. And it should be mentioned that in massive ablation of the placenta such as occurred in this case, shock is a much more common cause of death than hemorrhage. For confirmation of these opinions, I would suggest that Dr. Brody consult Sheehan¹ or Moon.² Both are eminent authorities on deaths due to shock.

Puerperium

Coryell, M. N., Harris, M. E., Miller, S., Williams, H. H., and Macy, I. G.: Metabolism of Women During the Reproductive Cycle XIV. The Utilization of Pantothenic Acid During Lactation, *J. Lab. & Clin. Med.* 32: 1454, Dec., 1947.

Metabolic studies of pantothenic acid intake and output were carefully performed in lactating women. The output in milk and urine was measured during the immediate puerperium and also at a later period, when lactation was well established. During the first ten postpartum days, pantothenic acid secretion in the milk was constant, its steady total increase being related to increasing milk volume produced. During the first five-day period, most subjects excreted less pantothenic acid in the urine than they took in their diet, while the reverse was true in the second five-day period. The authors conclude that pantothenic acid may be stored in the body or that it may be retained for more than twenty-four hours during its metabolism. They also state that physiologic levels are maintained in the milk and urine of such women, without respect to their current intake, if their nutritional status in respect to vitamins is good.

S. B. GUSBERG.

Coryell, M. N., Harris, M. E., Miller, S., Rutledge, M. M., Williams, H. H., and Macy, I. G.: Metabolism of Women During the Reproductive Cycle. XV. The Utilization of Biotin During Lactation, *J. Lab. & Clin. Med.* 32: 1462, 1947.

Careful metabolic studies of biotin intake and output in urine and milk were made in lactating women. The values for biotin in breast milk during the first four postpartum days were too low to be reliable. During the second five-day period, the total secretion and relative concentration in the milk varied widely. Studies of milk obtained at later periods, when lactation was well established revealed it to contain 2 to 14 per cent of the total intake. The urinary biotin excretion averaged 47 per cent of the intake during this period. The authors cite the work of other investigators, who have demonstrated a fecal biotin factor in biotin metabolism; they suggest that variation in fecal synthesis may explain the variability of individual response.

S. B. GUSBERG.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society. (1876) *President*, Ludwig Emge. *Secretary*, Norman Miller, Ann Arbor, Mich. Next meeting, May, 1949, Hot Springs, Va.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President*, A. D. Campbell, Montreal, Quebec. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.
- Central Association of Obstetricians and Gynecologists. (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists. (1938) *President*, S. R. Norris, Jacksonville, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Williamsburg, Va., February 10 to 12, 1949.
- A. M. A. Section on Obstetrics and Gynecology. *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
- New York Obstetrical Society. (1863) *President*, Albert H. Aldridge. *Secretary*, Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia. (1868) *President*, John B. Montgomery. *Secretary*, James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society. (1878) *President*, Aaron E. Kanter. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society. (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society. (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society. (1876) *President*, Stanley T. Garber. *Secretary*, Joseph G. Crotty, 146 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society. *President*, W. O. Johnson. *Secretary*, W. E. Oldham, 842 Barrett Avenue, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology. *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society. (1934) *President*, James Hodgkiss. *Secretary*, Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.
- Obstetrical Society of Boston. (1861) *President*, Paul Gustafson. *Secretary*, H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society. (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society. (1931) *President*, Henry N. Shaw. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.
- Washington Gynecological Society. (1933) *President*, William J. Cusack. *Secretary*, John Parks, 901 23 St., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society. (1924) *President*, Woodward D. Beacham. *Secretary*, Harry Meyer, Audubon Bldg., New Orleans 16, La. Meetings held October, November, January, March, and May.
- St. Louis Gynecological Society. (1924) *President*, Joseph A. Hardy, Jr. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

Since the publication of my paper, "The Conservative Management of Some Varieties of Placenta Previa," three years ago, approximately 7,500,000 babies have been born in continental United States. Assuming that the incidence of placenta previa is 1 in 180 term or near-term deliveries, there should have been 41,666 cases of all varieties of previa during this time. I am still sure that some of these cases, apart from those of placenta previa accreta, have, without manipulation, "bled to death," and I am still going to endeavor to find some of these cases in order to determine its incidence. With our better medical recording and with proper assistance from the numerous Maternal Mortality Committees, and, may it be added, with the same interest as shown by Dr. Brody, some cases should be uncovered. I am still of the opinion that the textbook picture of placenta previa is too frightening, and that the doctor who quickly says, "Oh, I know of a case, etc.," is probably dealing more in folklore than in facts.

I hope the publication of this correspondence will stimulate further interest.

HERMAN W. JOHNSON, M.D.

DEPT. OF OBSTETRICS,
BAYLOR UNIVERSITY
COLLEGE OF MEDICINE,
HOUSTON, TEXAS,
March 8, 1948.

References

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2. Moon, V. H.: Shock, Its Dynamics, Occurrence and Management, Philadelphia, 1942, Lea and Febiger.

- New Jersey Obstetrical and Gynecological Society. (1947) *President*, Herschel Murphy. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society. (1947) *President*, Colin C. McCorriston. *Secretary-Treasurer*, K. S. Tom, 296-E South Vineyard Street, Honolulu 39, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists. *President*, Duncan R. Neilson. *Secretary-Treasurer*, David M. Baker, 520 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies. (1947) *President*, William Benbow Thompson. *Secretary*, Woodward D. Beacham, 1430 Tulane Ave., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society. (1937) *President*, P. K. Champion. *Secretary*, L. J. Lohr, 2676 Salem Ave., Dayton, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.

- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Warren E. Massey. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Harold C. Maek. *Secretary*, John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Raymond J. Pieri. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Roger E. Stewart. *Secretary*, Albert F. Lee, 1115 Boylston, Seattle 1, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, J. M. Freeman. *Secretary-Treasurer*, Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, John Boyd. *Secretary-Treasurer*, William Durwood Suggs, Monument Ave. and Lombardy St., Richmond, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Dana Cox. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Austin B. Johnson. *Secretary*, Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, H. J. Lesniek. *Secretary*, Mark Daniel, 2344 Davidson Ave., Bronx 53, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima, Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Thomas J. Sims. *Secretary*, LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, Carl E. Krugmeier. *Secretary-Treasurer*, A. M. McCausland, 3780 Wilshire Blvd., Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, S. B. Conger. *Secretary-Treasurer*, Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.
- Minnesota Society of Obstetrics and Gynecology.** *President*, Everett C. Hartley. *Secretary*, John Haugen, 100 E. Franklin Ave., Minneapolis, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Charles F. Moon. *Secretary*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Le Roy H. Sadler. *Secretary-Treasurer*, John W. Records, 301 Northwest 12 Street, Oklahoma City.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

He began his professional career in Edinburgh as a general practitioner, but early devoted his attention to Midwifery, obtaining an appointment to the Lying-in Hospital and starting a lecture course for students in obstetrics.

When he was 28 years of age, the Professorship of Midwifery in the University became vacant and Simpson was a candidate for the Chair. The appointment was in the hands of the Town Council of the City and the contest for votes between Simpson and his chief rival, Kennedy of Dublin, was very keen. Simpson put all of his enormous energy into the fight, even going so far as to acquire a wife at short notice when he learned that his state of bachelorhood was being used as an argument against him. He was finally elected to the Chair by the margin of one vote.

We are apt today to think that Simpson's only claim to fame rests upon his contributions to the knowledge and practice of general anesthesia and its application in obstetrics. But had he done nothing at all in this field, his name would still live as one of the pioneers in the fields of both obstetrics and gynecology. He was a great teacher, both as a lecturer to his students and as a contributor to medical journals. His collected papers fill three very large, closely printed volumes. He was a great antiquarian. He had a command of the English language which is perfectly remarkable and he used this gift in controverting the criticisms to which his plea for anesthesia in labor gave rise.

He is the inventor of the uterine sound and wrote several papers on its use in diagnosis. He gave a most accurate description of the mechanism of labor in the rickety flat pelvis.

A contemporary of Oliver Wendell Holmes, he believed with him that puerperal infection "is usually propagated, not directly from individual to individual, but indirectly through the medium of a third person; and that person generally the medical attendant or nurse." He wrote much on surgical sepsis or surgical fever, as it was then called, and believed that much of it was due to the aggregation of patients in hospitals.

He and Lister were working in Edinburgh at the same time but we have to record that Simpson never accepted the Listerian concept of the bacterial origin of septic infection—a remarkable weakness in one otherwise so strong.

I have mentioned only a few of the topics on which Simpson wrote. Somewhere in the three volumes of his papers we can find his views on practically every obstetric and gynecologic subject which is under discussion today.

This evening, however, it is his work on obstetric anesthesia which especially interests us because it was just 100 years ago on last January 19th, that Simpson administered for the first time inhalation anesthesia with ether to a woman in labor. That date, January 19th, 1847, is therefore a notable one in obstetric history. Later in the same year, on November 4th, Simpson discovered the anesthetic properties of chloroform. On November 10th he read a paper at the Edinburgh Medico-Chirurgical Society entitled "An account of a New Anesthetic agent as a Substitute for Sulphuric Ether in Surgery and Midwifery." This paper was published on Nov. 15, 1847.

With all his enormous mental drive and scientific outlook, Simpson was a man of fine sensibilities. When a student, he almost gave up medicine for law,

American Journal of Obstetrics and Gynecology

VOL. 56

AUGUST, 1948

No. 2

Special Article

COMMEMORATION OF THE CENTENNIAL OF THE INTRODUCTION OF ANESTHESIA IN OBSTETRICS BY SIR JAMES Y. SIMPSON*

B. P. WATSON, M.D., F.R.C.S.E., F.R.C.O.G., NEW YORK, N. Y.

IT IS a great privilege to speak on this occasion, when the New York Obstetrical Society commemorates the Centennial of the Introduction of Anesthesia in Obstetrics by Sir James Y. Simpson, for Simpson is one of my heroes.

He died long before I was born, but I was house surgeon to his nephew and successor, Sir Alexander Simpson, who often talked to me about him. I have dined in the same dining room and off the same table round which Simpson and his friends gathered when they tested out on themselves the effects of various agents which might have anesthetic properties and ultimately found chloroform. I occupied for four years the professorial Chair of Midwifery and Diseases of Women in the University of Edinburgh, the chair to which Sir James Simpson has given distinction for all time. For these reasons I have a very personal feeling for him and for all that he did. So much so, that I took him as the subject of part of my inaugural address as President of the American Gynecological Society. My talk to you tonight may therefore be somewhat repetitious, and for this I ask your indulgence.

Simpson's contribution to the alleviation of human suffering arose in no haphazard fashion. He was a man of great mental capacity and was endowed with a true scientific spirit. Already as a schoolboy, the seventh son of poor parents, he had studied the flora and geology of the countryside. He was head of his school at the age of fourteen when he entered the faculty of Arts of the University of Edinburgh. He never completed his Arts course for after two years he was attracted to medicine. He completed his medical course and passed the final examination at the age of 19 and had to wait two years before he could be graduated and be licensed to practice. These two years were occupied in attending again the course in Midwifery, in acting as assistant to the professor of pathology, in assisting the doctor in his native village of Bathgate and in travel to London and the continent of Europe.

*Read at a meeting of the New York Obstetrical Society, Dec. 9, 1947.

November 4th, 1847—on returning home after a weary day's labor, Dr. Simpson with his two friends and assistants, Dr. Thomas Keith and J. Matthews Duncan, sat down to their somewhat hazardous work in Dr. Simpson's dining room. Having inhaled several substances, but without much effect, it occurred to Dr. Simpson to try a ponderous material, which had been formerly set aside on a lumbar table, and which, on account of its great weight, he had hitherto regarded as of no likelihood whatever. That happened to be a small bottle of chloroform. The bottle was searched for, and recovered from beneath a heap of wastepaper. And, with each tumbler newly charged, the inhalers resumed their vocation. Immediately an unwonted hilarity seized the party; they became bright-eyed, very happy and very loquacious—expatiating on the delicious aroma of the new fluid. The conversation was of unusual intelligence, and quite charmed the listeners—some ladies of the family and a naval officer, brother-in-law of Dr. Simpson. But suddenly there was a talk of sounds being heard, like those of a cotton mill, louder and louder; a moment more, then all was quiet, and then—a crash.

“On awakening, Dr. Simpson's first perception was mental, ‘This is far stronger and better than ether,’ he said to himself. His second was to note that he was prostrate on the floor, and that among the friends about him there was both confusion and alarm. Hearing a noise, he turned round and saw Dr. Duncan beneath a chair—his jaw dropped, his eyes staring, his head bent half under him; quite unconscious, and snoring in a most determined and alarming manner. More noise still, and much motion. And then his eyes overtook Dr. Keith's feet and legs making valorous efforts to overturn the supper-table, or more probably to annihilate everything that was on it; I say, more probably, for frequent repetitions of inhalation have confirmed, in the case of my esteemed friend, a character for maniacal and unrestrainable destructiveness, always under chloroform, in the transition stage. By and by, Dr. Simpson having regained his seat, Dr. Duncan having finished his uncomfortable and unrefreshing slumber, and Dr. Keith having come to an arrangement with the table and its contents, the sederunt was resumed. Each expressed himself delighted with the new agent, and its inhalation was repeated many times that night—one of the ladies gallantly taking her place and turn at the table—until the supply of chloroform was fairly exhausted.”

There can now be no question but that to Simpson belongs the sole credit of being the first to suggest and to use general inhalation anesthesia with ether in labor and that he was the first to demonstrate the anesthetic property of chloroform. While time has not confirmed Simpson's assertion that chloroform was a better and safer anesthetic than ether, some of us still regard it as having a very definite place in obstetrics.

The first mother to receive chloroform anesthesia during labor was the wife of Dr. Carstairs of Edinburgh. The child, a girl, was named “Anaesthesia.” Her portrait at the age of 17 stood on Simpson's desk, and he called her his patron saint, “St. Anaesthesia.”

after witnessing the agony of a patient undergoing a surgical operation in the Royal Infirmary. The suffering of his parturient patients always distressed him. He tried all sorts of drugs and even resorted to experiments in hypnotism in an effort to relieve them. Among all his other interests this one was ever present in his mind. When, therefore, news reached Edinburgh from across the Atlantic that Morton, in Boston, on Oct. 16, 1846, had successfully induced anesthesia by inhalation of ether in patients operated on by Bigelow and others, and that Liston had subsequently used it in London, Simpson was thrilled and immediately thought of its possibilities in obstetrics.

The problem that faced him was a harder one than that which confronted the surgeon. In those days, the surgeon did his work quickly, so that the patient did not require to be long under the influence of the anesthetic. The problem presented to Simpson was twofold. Could the anesthesia be continued sufficiently long to give appreciable relief? And would the anesthetic interfere with uterine contractions? He chose for the first trial a case of contracted pelvis, calling for the operation of version. He waited for this case, because, from the nature of the operation, any interference with the uterine contraction by the anesthetic would be of little moment. On Jan. 19, 1847, the operation was successfully and painlessly performed under ether anesthesia, and Simpson was able to satisfy himself that uterine contraction went on normally. He, therefore, proceeded to employ it in normal cases, an account of which he read before the Edinburgh Obstetrical Society on Feb. 10, 1847. The practice was soon taken up in Scotland, in France, in England, in Germany, and a few months later in America.

Not being altogether satisfied with ether, because of the large quantities required in prolonged cases, and because of the bronchial irritation to which it often gave rise, he had sent to him by different chemists various volatile substances which might be inhaled. With these he experimented on himself and on his friends. Amongst these substances was a small quantity of chloroform. It is said that Mr. Waldie, a Scotsman in business as a chemist in Liverpool, had suggested to him that this was probably the anesthetic substance in the chloric ether which Bigelow in Boston and Liston and Jacob Bell in London had used successfully.

In a recent letter to the British Medical Journal, Dr. Selby states that Dr. Matthews Dunean told him that it was he, Dunean, who found a bottle of chloroform in Dr. Gregory's chemical laboratory in Edinburgh University and conveyed it to Simpson's house. The substance, chloroform, had been discovered independently in this country, in France, and in Germany, in the year 1831.

Here is the story of the discovery, of its anesthetic properties as it is graphically told by Professor Miller, a near neighbor of Sir James Simpson in Queen Street, Edinburgh, and quoted by his nephew and successor in the Chair, the late Sir A. R. Simpson. As a contemporary account I think it is worth quoting again.

"Most of these experiments were performed after the long day's toil was over—at late night or early morn—and when the greater part of mankind was soundly anaesthetized in the arms of common sleep. Late one evening—it was

I quote its concluding paragraph because it puts in a nutshell the sequence of events in the discovery of anesthesia. Here are Simpson's words:

"If we try to put into a summarized form the data which we have been discussing regarding the introduction of anesthesia in America and this country, it appears to me that we might correctly state the whole matter as follows:

"1—That on the 11th December, 1844, Dr. Wells had, at Hartford, by his own desire and suggestion, one of his upper molar teeth extracted without any pain, in consequence of his having deeply breathed nitrous oxide gas for the purpose, as suggested nearly half-a-century before by Sir Humphrey Davy.

"2—That after having with others proved, in a limited series of cases, the anesthetic powers of nitrous oxide gas, Dr. Wells proceeded to Boston to lay his discovery before the Medical School and Hospital there, but was unsuccessful in the single attempt which he made, in consequence of the gas-bag being removed too soon, and that he was hooted away by his audience, as if the whole matter were an imposition, and was totally discouraged.

"3—That Dr. Wells' former pupil and partner, Dr. Morton of Boston, was present with Dr. Wells when he made his experiments there.

"4—That on the 30th September, 1846, Dr. Morton extracted a tooth without any pain whilst the patient was breathing sulphuric ether, this fact and discovery of itself making a New Era in anesthetics and in surgery.

"5—That within a few weeks (October 16th) the vapour of sulphuric ether was tried in a number of instances of surgical operations in Boston—Dr. Morton being generally the administrator; and ether vapour was established as a successful anaesthetic in dentistry and surgery.

"6—That in January, and the subsequent spring months, 1847, the application of sulphuric ether as an anesthetic in midwifery was introduced (by me), described in our medical journals, and fully established in Edinburgh, before any case with it was tried in Boston or America.

"7—That on the 15th November, 1847 (that is the date of the publication of his paper), the anesthetic effects of chloroform were discovered in Edinburgh, and that it swiftly superseded in Scotland and elsewhere the use of sulphuric ether, and extended rapidly and greatly the practice of anesthesia in surgery, midwifery, etc."

The letter continues: "I am very sorry to have taken up so much of your time and my time with such a petty discussion as the present. It has extended to too great length; but I am a sad invalid just now, and quite unable to write with the force and brevity required. With many of our profession in America I have the honour of being personally acquainted, and regard their friendship so very highly that I shall not regret this attempt—my last perhaps—at professional writing as altogether useless on my part, if it tends to fix my name and memory duly in their love and esteem.

"Yours very truly, J. Y. Simpson."

The news of Simpson's death reached Boston by cable before his letter arrived and the Gynecological Society of Boston held a Memorial Meeting in honor of their "late beloved associate" who was, they said, "one of nature's noblemen."

Thus the ultimate result was that Simpson freely acknowledged—as he had always done—that he believed that Morton was the first man to produce general anesthesia to the surgical degree by the administration of ether, and Bigelow acknowledged that Simpson was the first man to use ether as an anesthetic in obstetrics and that he discovered the anesthetic properties of chloroform.

You will note that neither of them makes any mention of Jackson, although Simpson, in some of his earlier writings, does note that it was he who had sug-

With the demonstration of the feasibility of general anesthesia in the conduct of labor, Simpson's work was not finished, for there immediately arose a most determined opposition to its use from certain members of the medical profession and from the Church. One could spend a whole evening quoting Simpson's forceful replies to all types of criticism—none was too trivial for him to pass over. For instance, take the following extract from one of his letters:

“Edinburgh, February, 1849.

“An objection to the employment of chloroform in midwifery, on the ground of alleged indecencies committed by patients whilst under its influence, has been raised by Mr. Gream. This is by no means a new objection. At the time when various of our now common articles of food and medicine were first introduced into use, these innovations were frequently opposed and decried on exactly the same ground. As a general rule, this was an argument always resorted to by weak and impure minds, when they could find no stronger arguments against any proposed innovation in our customs or habits. For instance, at the present day, no one imagines or argues that the eating of potatoes is liable to cause in those who eat them any indecency of word or action. And yet that was one of the principal arguments maintained by the unscrupulous against the use of potatoes for long after their introduction. In his ‘Traditions,’ Mr. Chambers states that, even as late as the last century, there was a prejudice against the potato for this, among other reasons—‘That it was a provocative to incontinence.’ A hundred years after this, our successors in the profession will probably feel as much surprised at the idea of the use of chloroform exciting improper words and actions, as we are all now at the old idea of the use of potatoes being attended with the same alleged consequences.”

I think that we, his successors, one hundred years after, can say to the shade of Simpson tonight that we certainly are surprised.

His two chief medical opponents in this country were Meigs of Philadelphia and Bigelow in Boston. Between Meigs and Simpson the point at issue was whether it was right and proper to relieve a woman of the pains of labor by general anesthesia. Meigs maintained the attitude taken by many clergies of that day that to do so was to go against nature and against a divine dispensation. Meigs wrote that he regarded “The pain of natural labor as a state not by all possible means and always to be eschewed and obviated, a labor pain being a most desirable, salutary, and conservative manifestation of life force.” He also objected to anesthesia in forceps deliveries on the ground “that the Sensations of the patient afford us our best aid for the introduction of the instrument.”

The controversy between Dr. Jacob Bigelow of Boston and Simpson was as to the priority of the discovery of general anesthesia and its use in obstetrics. Bigelow accused Simpson of not duly recognizing Morton, and Simpson accused Bigelow and others in Boston of not recognizing him (Simpson) as the first man to give general anesthesia to a woman in labor. Their letters extend to many printed pages and make most lively reading. The last letter was written by Simpson from Edinburg in April, 1870.

Another described him as possessing: "The head of Jove, the body of Bacchus."

James Young Simpson conferred upon women a great blessing. But it was not at first an unmixed blessing. The general use of anesthesia was followed not by a diminution but rather by an increase in maternal mortality. Milne Murray of Edinburgh, writing in the year 1900, said, "I feel sure that an explanation of much of the increase of maternal mortality from 1847 onwards will be found in, first, the misuse of anesthesia, and, second, the ridiculous parody which, in many practitioners' hands, stands for the use of antiseptics. Before the days of anesthesia, interference was limited and obstetric operations were at a minimum, because interference of all kinds increased the conscious suffering of the patient. When anesthesia became possible, and interference became more frequent because it involved no additional suffering, operations were undertaken when really unnecessary, on the demand of the patient or for the convenience of the practitioner. And so complications arose and the dangers of labor increased."

We have gone a long way since these words were written, forty-seven years ago. We have got newer and better analgesics and anesthetics, and a better understanding of their use, whilst the profession at large has been educated out of the era of "meddlesome midwifery," with the result that today maternal mortality is at an all-time low in this and in many other countries.

This result could not have been achieved without our analgesic and anesthetic agents. As domiciliary midwifery has gradually been superseded by hospital obstetrics, our aseptic techniques have been perfected until they are on a par with those of general surgery. This, together with the use of the sulphonamides and penicillin, accounts for much of the fall in maternal mortality. The meticulous carrying out of these techniques would be extremely difficult or impossible with a restless patient.

But we must be careful not to go to extremes and yield to the clamor of uninformed lay demand as expressed in certain of our popular magazines and newspapers for absolutely painless labor for all women. If we do so, we may have a repetition of the events which followed in 1847.

No honest obstetrician can ever promise to any woman an absolutely painless labor. He can promise to make her labor as painless as possible consistent with safety to herself and to her child. He cannot, beforehand, accede to a request for some particular form of pain relief. He must reserve to himself the choice of which method he will use and at what stage in labor he will use it according to circumstances.

The greatest honor we can pay today to the memory of Sir James Young Simpson is to use and not abuse the gift he gave us.

gested ether as an anesthetic to Morton; nor is Long mentioned, and yet there seems to be no doubt that it was Long who, in 1842, first used ether as an anesthetic in the performance of a surgical operation.

The controversy among these five men, Crawford W. Long, Horace C. Wells, William T. S. Morton, Charles T. Jackson and James Young Simpson extended over many years. Their rival claims were supported by a host of protagonists, most of them willfully blind to the opposing facts and many of them swayed by geographical and national prejudices. Morton, Wells, and Jackson were Northerners and Long was a Southerner. Is it to be wondered at that, during the period when the Civil War was brewing, boiling over, and ended, the Southerner was forgotten and ignored by the triumphant North? Or was it strange that all should combine against the claims of the foreigner?

So far as the principals were concerned, it ended in tragedy for the three Northerners who spent their time and their substance in fighting their claims against each other and getting nowhere. Wells committed suicide, Morton died in penury, and Jackson spent his last years and died in an insane asylum. Long, ruined by the War, rebuilt his fortunes as a practicing physician in Georgia and died in harness at a ripe old age.

Simpson alone had honors heaped upon him, but he died a comparatively young man, he was just 58—worn out by hard work. He was created a baronet; he enjoyed a very large and very lucrative practice, but never did he allow his active mind any rest. His writing was done at all hours of the day and night while waiting on the delivery of his patients. He lived to see the use of anesthesia in labor become general, a tremendous impetus to its acceptance being given when Queen Victoria gave birth to her two youngest children under the influence of chloroform. It was administered by Dr. John Snow, the first man in Britain to limit his practice to anesthesia.

I quote you a description, somewhat fulsome according to our present standards, given of Simpson when at the zenith of his powers, by one of his contemporaries.

"In stature the Professor is somewhat under the middle size. The roundness of his whole form and the absence of Scotch 'processes of bone' would authorize the inference of English extraction. His ambrosial locks, dark and almost imperceptibly shaded with red, fall upon his shoulders. No feature in the Professor's countenance is overgrown. The forehead is broad and projecting rather than lofty. There is much firmness about the mouth and the lips. The eye is brilliant, and looks out from the eyebrows with an energy and penetration betraying great mental power. With the fiercer radiation of its eagle fires is blended the soft glow of a warm heart, which gives it a decided intellectual and moral expression. There is a fascination in his air, manners and conversation, an irresistible moral gravitation which elicits and wins the admiration, love and confidence of all who come within the magic circle of its influence."

A medical colleague wrote in 1848: "Decidedly the most wonderful man of the age in which he lives is Simpson of Edinburgh. Nothing baffles his intellect, nothing escapes his penetrating glance, he sticks at nothing, he bungles nothing. From all parts, not of Britain only, but of Europe, do ladies rush to see, consult and fee the little man."

Point 2, placed four inches to the right of the umbilicus on a level with it; and to Point 3, placed four inches to the left of the midline and half the distance between the umbilicus and the left inguinal crease. The indifferent electrode (No. 4) was placed on the left thigh. (Fig. 1.)

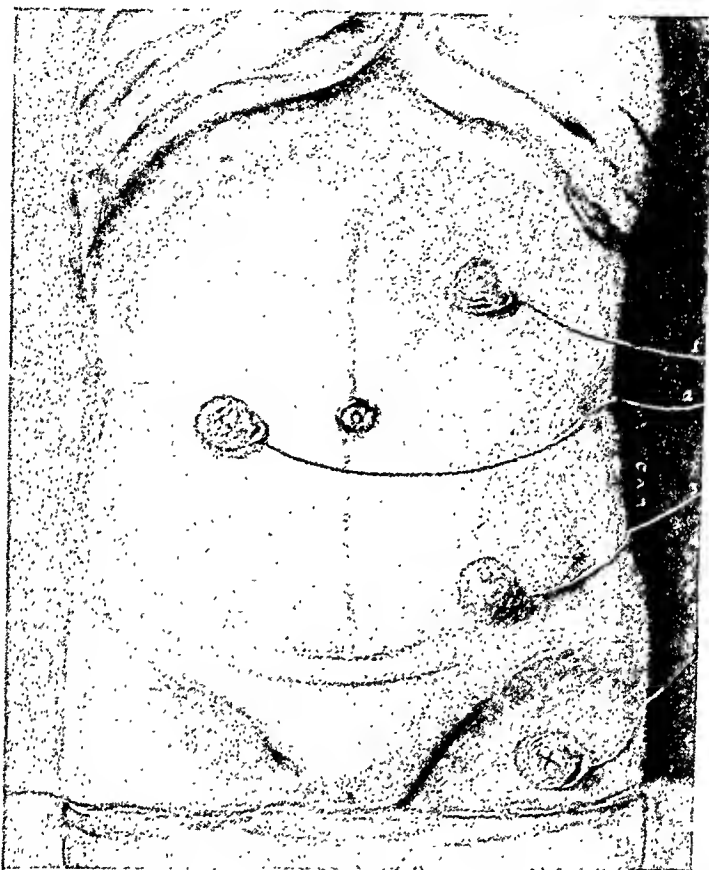


Fig. 1.—The placement of the abdominal electrodes and their numerical sequence is demonstrated.

Each of the three active abdominal electrodes was attached to the input terminal of a Type 715-A General Radio direct current amplifier by shielded wire. The indifferent electrode (No. 4) was connected to a suitable grounded object, as was each amplifier. The outputs of the three amplifiers were applied to the input terminals of Esterline-Angus supersensitive recorders (1 Ma. for 5-inch deflection), which were arranged to run synchronously by mechanical linkages. It was found necessary to arrange these instruments in order of rapidity of feeding the record, using the fastest as the lead instrument and the slowest one to provide drag, always starting the slowest last in order to synchronize the three instruments at the beginning of the records.*

*In our original note we stated that the recorder wrote at the rate of three inches a minute. Dr. Donald B. Lindsley, of the Department of Psychology of Northwestern University, Evanston, Illinois, to whom we are indebted for much helpful criticism, suggested that reduction for publication renders this measurement worthless. In explanation, we should like to point out that the distance between the curved lines on the record represents fifteen seconds.

We are also unable to put in calibrating voltages on each record because our samples are taken from representative areas in actual recording. One millivolt on all records, however, is represented by the space covered by four of the fine horizontal lines of the record.

Original Communications

FURTHER STUDIES ON THE ELECTRICAL POTENTIALS OF THE HUMAN UTERUS IN LABOR*

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DURING the investigation of the electrical phenomena associated with the human uterus in labor, it was found that changes in electrical potential, of low frequency and with an amplitude of several millivolts, could be recorded from the exterior of the abdomen.¹

This study was originally conducted with the purpose of determining the nature of action currents, their effect on the type of labor developed by the uterine musculature, and the diagnosis of any defects in pattern or voltages, if such patterns were found. Because of inherent difficulties in the amplifying and recording system employed, the uncertainties associated with skeletal muscular effects, and the failure to find a regularly reproducible pattern for these currents, extension of the methods was found necessary, with modification of the recording techniques.

The present communication is concerned with the presentation of these findings.

Materials and Methods

Over forty patients were included in the series; complete records were obtained on thirty-one cases and the remaining ones discarded because of incompleteness, lack of cooperation of the patient, or mechanical difficulties which made the value of the recording uncertain.

Labor was investigated in eighteen of the patients under varying stages of analgesia produced by barbiturates, Demerol and seopolamine. Sedation varied from an almost negligible degree to the extent of having the patient motionless during contractions. Thirteen patients were studied, in whom caudal block was used as the means of pain relief.

In this study, it was planned to record simultaneously the current from three points on the abdominal wall, in order to determine the presence or absence of a path of current spread and, at the same time, to calculate the increment or decrement of voltage along the points of this path.** Saline electrodes with platinum contacts were applied by means of collodion to Point 1, placed four inches to the left of the midline and four inches above the umbilicus; to

*The opinions expressed here are those of the authors and do not necessarily reflect those of the Navy Department.

**Three points were utilized as a minimum with which the direction of the path of spread could be determined and an optimum in so far as equipment and electrode distribution are concerned.

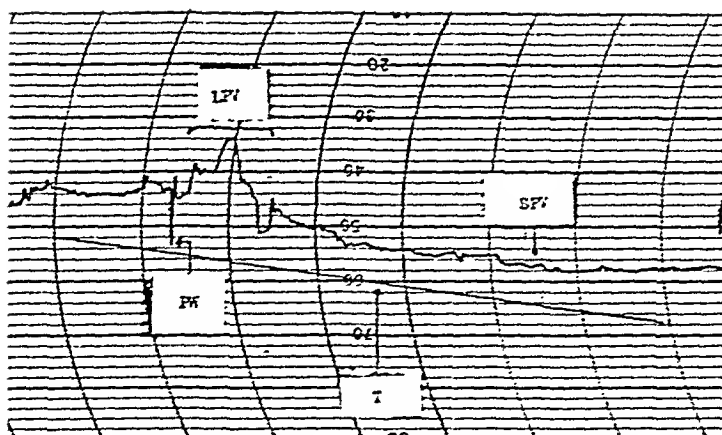


Fig. 2.—A curve demonstrating the types of variations in voltages and the terminology assigned to each variation.

T (trend): long term changes in voltages measured by the angle of deviation from the horizontal over a period of minutes.

LPV (long period variation): changes in voltage which occupy several seconds (characteristically 5 to 20 seconds).

SPV (short period variation): changes in voltage which occupy a few seconds (characteristically 2 to 5 seconds).

PW (pulse wave): sudden bursts of voltage approaching one second in duration with a rapid return to the original voltage level.

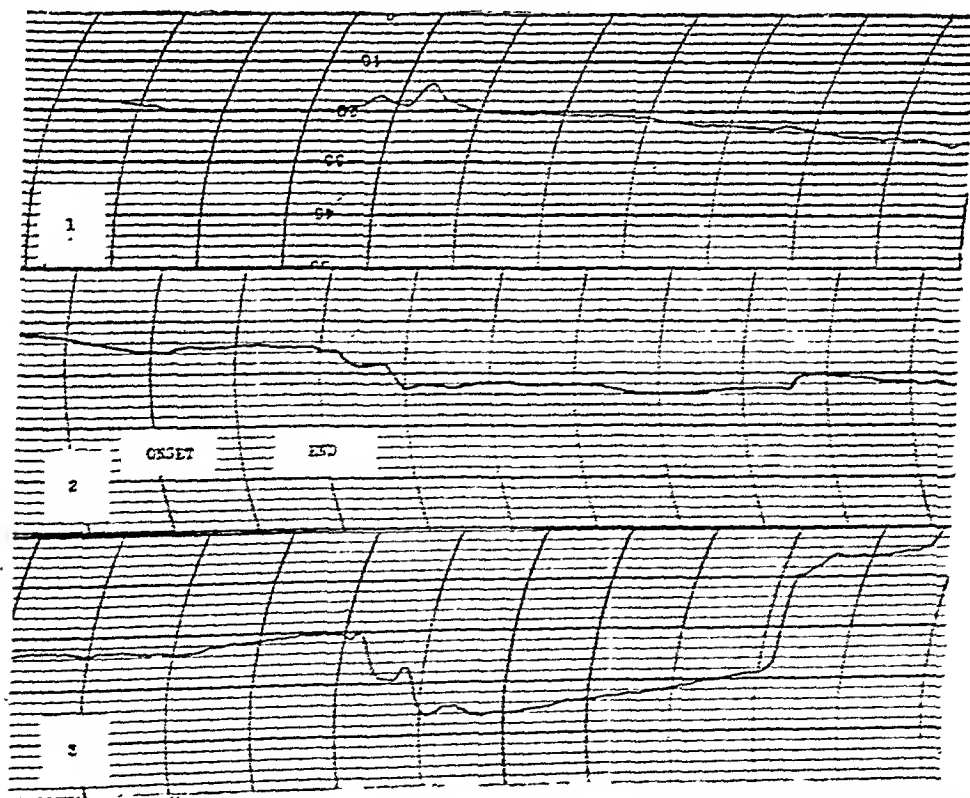


Fig. 3.—Painless contractions of prelabor. These records, obtained synchronously, vary so in voltage level, in trend, and in long period variation, that they cannot be recognized as coming from the same patient. Pulse waves are absent from all, and short period variations are noted only in Lead III, and even here voltage variation for this wave is extremely small.

Notations of contractions, motion, electrical static, type of labor, degree of cervical dilatation, palpation, rectal examination, technical details, and medications were made directly on the recording paper.

Since there was no easily recognizable pattern due to uterine contraction or uterine mechanical activity, it was thought necessary to classify the varying changes in potential with respect to the time necessary to complete a cycle. Fig. 2 is a representative tracing illustrating the typical changes. Classifications of the changes in potential associated with smooth-muscle activity have been made by Rosenblueth and coworkers² and by Eccles and Magladery.³ Their work was done on organ strips of laboratory animals with electrodes placed directly on the source, and are of very short interval (a few milliseconds). We do not feel that the patterns we have described are analogous to those of Rosenblueth and Eccles because of the greatly increased interval.

Trend (T) can be classified as a slow, gradual change in potential in either direction: in a relative negative sense with respect to the indifferent electrode (upward), or in a relative positive sense with respect to the indifferent electrode (downward). Actually, this slow change of potential is a very long period variation, occupying several minutes rather than a few seconds, and is not an entirely different phenomenon from the other changes noted.

We have classified slow changes in potential in either direction which arbitrarily occupy approximately ten to thirty seconds as "long period variations" (L.P.V.), and those which occupy three to five seconds as short period variations (S.P.V.).

An additional phenomenon, called a "pulse wave" (P.W.), is noted when a static charge is communicated to the body or to the recording instrument, but the wave also occurs spontaneously, apparently from the uterine musculature. It is of very short duration, about one second, and is of relatively high voltage (several millivolts). It is to be re-emphasized¹ that the recorder used will not, under ordinary circumstances, respond to changes of potential of less than one second's duration, because of the mechanical inertia built into the recorder.

Results

Group I (Two patients).—Painless contractions with impending onset of labor.

Both patients were multiparas at term with the fetal head engaged and the cervix 2 to 3 cm. dilated. They were considered to be safe candidates for the induction of labor by artificial rupture of the membranes. In this manner we could be assured of obtaining tracings on patients in the very earliest phases of true labor.

Electrodes were applied at the designated positions and control tracings obtained. The membranes were ruptured under sterile precautions and recordings made until the contractions became painful.

Fig. 3 is a typical recording of such a patient. It is noted that the contraction in this record was maintained for thirty seconds, and clinically was felt to be of moderate tension. Voltage changes in all three leads are minimal during the contraction and most noticeable following it. The most striking points, however, are the absolute lack of similarity of the pattern in each of the leads, and the fact that, even though changes in voltage of noticeable magnitude do occur, they are asynchronous and in no way do they give the impression that they could have been taken from the same patient.

The trend of Leads I and II is downward while that of Lead III is upward. Short period variations are absent from all leads and long period variations are inconstant and infrequent. No pulse waves are present.

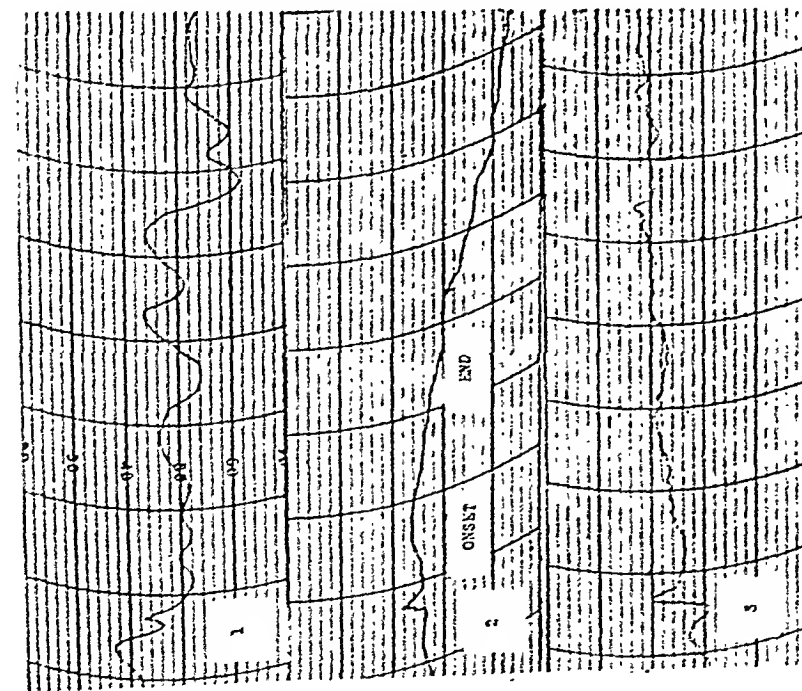


Fig. 4.

Fig. 4.—Painless contractions associated with early labor. Voltage variations are quite different in each lead although trends in Leads I and II are similar. Trend of Lead III is opposite in phase. Long period variations are noticeably different in all leads, and short period variations are definitely recognizable only in Lead I. Pulse waves of very low amplitude are occasionally seen.

Fig. 5.—Early labor with painful contractions. Recognizable similarity of configuration in all leads is present. The trend of each curve is slightly but definitely different. Long period variations are similar but not identical, and short period variations are much less noticeable in Lead I. Pulse waves are occasionally seen but are of very low voltage.

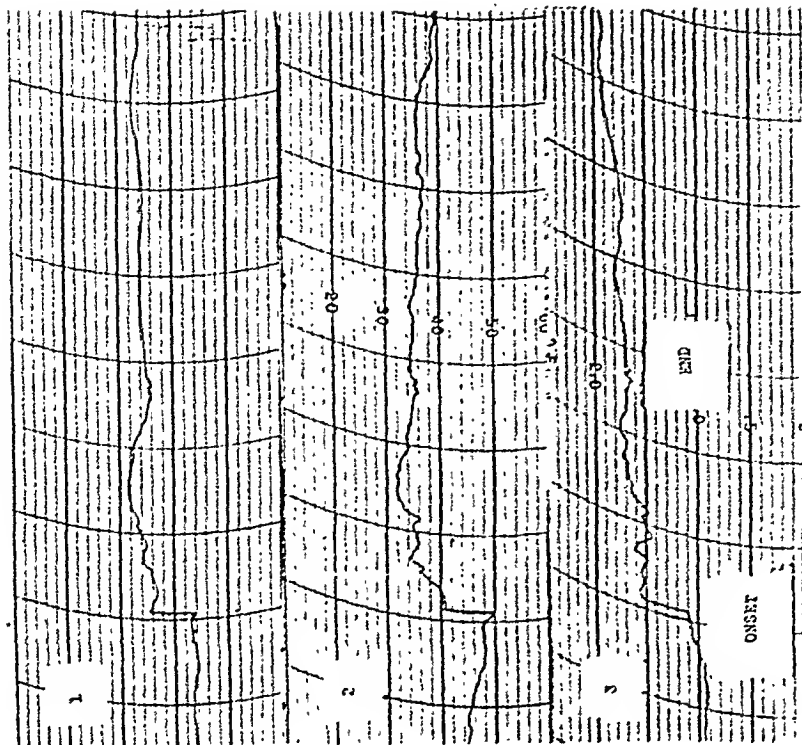


Fig. 5.

Interpretation: In prelabor, the electrical activity of the uterus is not generalized or coordinated. Changes in potential are small and infrequent; they are most evident over the lower uterine segment. Standing potentials, or basic potential differences, are grossly irregular when one area of the uterus is compared with another area.

*Group II (Five patients).—*Early labor associated with painless or mildly painful contractions without progressive cervical dilatation.

Two of these patients were primiparas in early labor of spontaneous origin. At the onset of recording, the contractions were painless, and, toward the end, were bearable but definitely painful. The third was a multipara in whom progress was prevented by heavy sedation with barbiturates and Demerol after a 5 cm. dilatation of the cervix had been experienced.

Fig. 4 is a typical record of what is clinically designated as false labor, defined arbitrarily as irregular contractions both in duration and interval, without progressive dilatation of the cervix.

It is noted here that although Leads I and III are active with frequent changes of voltage, Lead II is relatively quiet. The trend of Leads I and II is similar although Lead III is in the opposite direction. Long period variations are outstanding in Lead I and short period variations are the outstanding feature of Lead III. An occasional pulse wave is seen in this type of labor. Dissimilarity of the leads is the outstanding feature of this picture.

Interpretation: Nonprogressive mild labor, or "false labor," is characterized by definite changes in potential, but these changes are not coordinated and differ widely in varying areas of the musculature. Standing potentials, here, too, are dissimilar. Short period variations are most marked over the lower uterine segment.

*Group III (Five patients).—*Early painful contractions associated with slow dilatation of the cervix.

These patients, three primiparas and two multiparas, were in early progressive labor of mild to average intensity. Sedation was absent or, at most, enough to produce slight drowsiness.

Fig. 5 is representative of the recordings of this type of labor. Here, for the first time, the synchronism of the records is recognizable and in general the patterns are similar. The trends of Leads I and II are similar, but Lead III is out of phase, although this is not always the case in this type of labor. Long period variations are recognizably similar in all leads; they are most evident in Lead III and least so in Lead I. Large changes in voltage are also most evident but occasionally occur in Leads I and II.

Interpretation: In mild, progressive labor, there is a distinct similarity in the changes of potential in all portions of the uterus. Small differences in localized areas may exist, but, in general, the changes in potential are well coordinated. The standing potential may or may not be identical.

*Group IV (Five patients).—*Patients with severe contractions and rapid dilatation of the cervix.

There were two multiparas and one primipara in this group. In this type of case, many records had to be discarded for the obvious reasons of poor cooperation of the patient, excessive motion, or uncertainty of recording. Three of these patients were extremely cooperative and, despite mild sedation, in the face of severe pain, restricted motion to a minimum.

Figs. 6 and 7 were obtained from these patients. It is noted here that changes in voltage in all leads were of good amplitude and that the records are grossly identical in trend, amplitude of voltage, long and short period variations, and in pulse waves.

All the patients on whom records were made with caudal anesthesia were in good progressive labor before the caudal was instituted; we did not feel justified in doing such a procedure purely to make a recording. Immediately after inception of the caudal, however, in several instances, labor became non-progressive for periods varying from one hour to several hours, and the four patients described in this group were of this type.

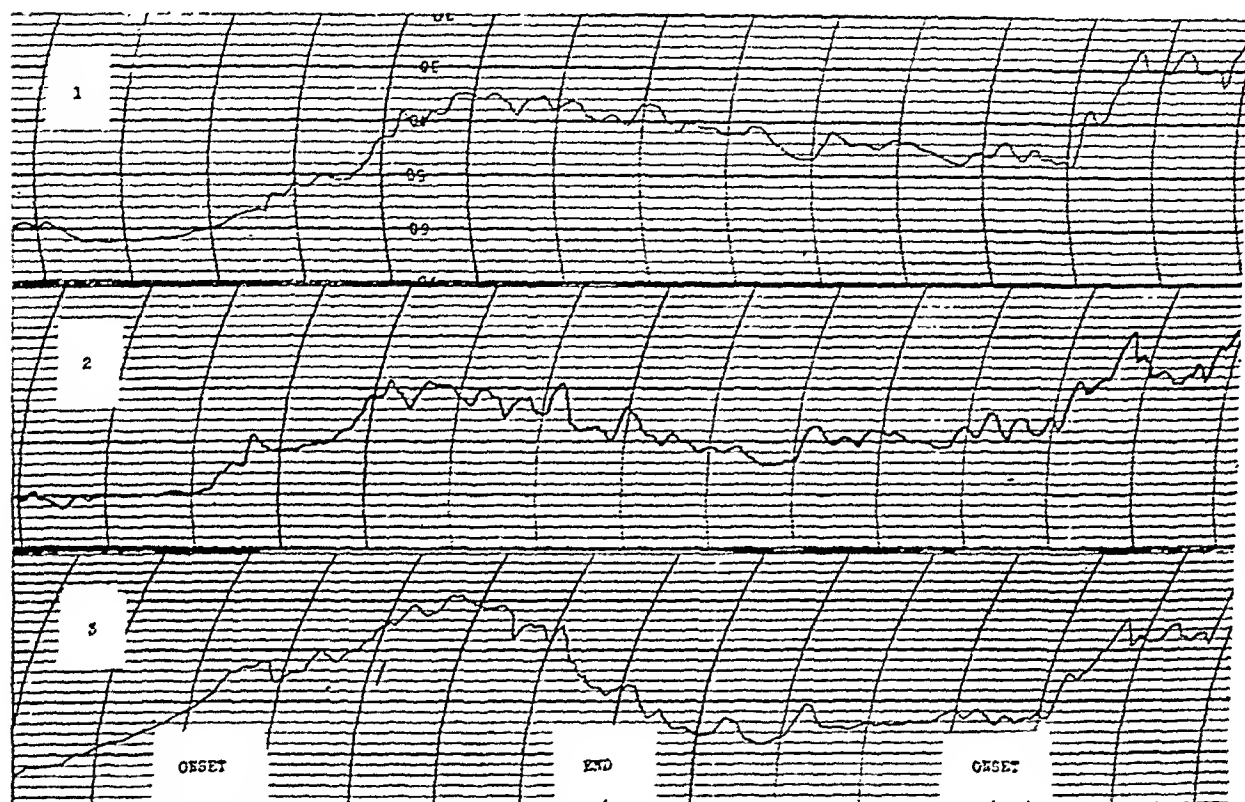


Fig. 7.—Severe labor. As in Fig. 6, all three leads are approximately identical

Fig. 8 is representative of such a patient. It is noticeable that Lead I is quite without definite changes in voltage save in trend, in which it equals Leads II and III. Long and short period variations are seen definitely in Leads II and III but definitely are not of the same pattern.

It is of interest that if only one lead had been used, placed in the position of No. 1 electrode, the picture would be that reported in our original description of the effect of caudal anesthesia on the changes in potential during labor. If the electrode had been placed in the position of Lead III, however, the picture obtained would have been quite different.

Short pulse waves are noted in all three leads, although, as in the case of the short period variations, they are most obviously in Lead III.

Interpretation: Caudal anesthesia may temporarily reduce the rate of progression of cervical dilatation, despite what seem to be adequate contractions of the uterus. In such a case, there is generally a gross difference in the change of potential in varying portions of the uterus, although, in general, the trend is still synchronous. The over-all effect of caudal anesthesia is that of blocking parasympathetic motor nerve impulses to the uterus, and is most in evidence in the fundus and least noticeable in the lower uterine segment, although it is definite in all areas.

Close scrutiny will show that certain wave forms are not identical, although in general each form can be identified on each lead. Short period variations are most sharply defined in Lead III and least in Lead II, while long period variations are best seen in Lead II and least marked in Lead I. Standing voltages in all leads are approximately the same.

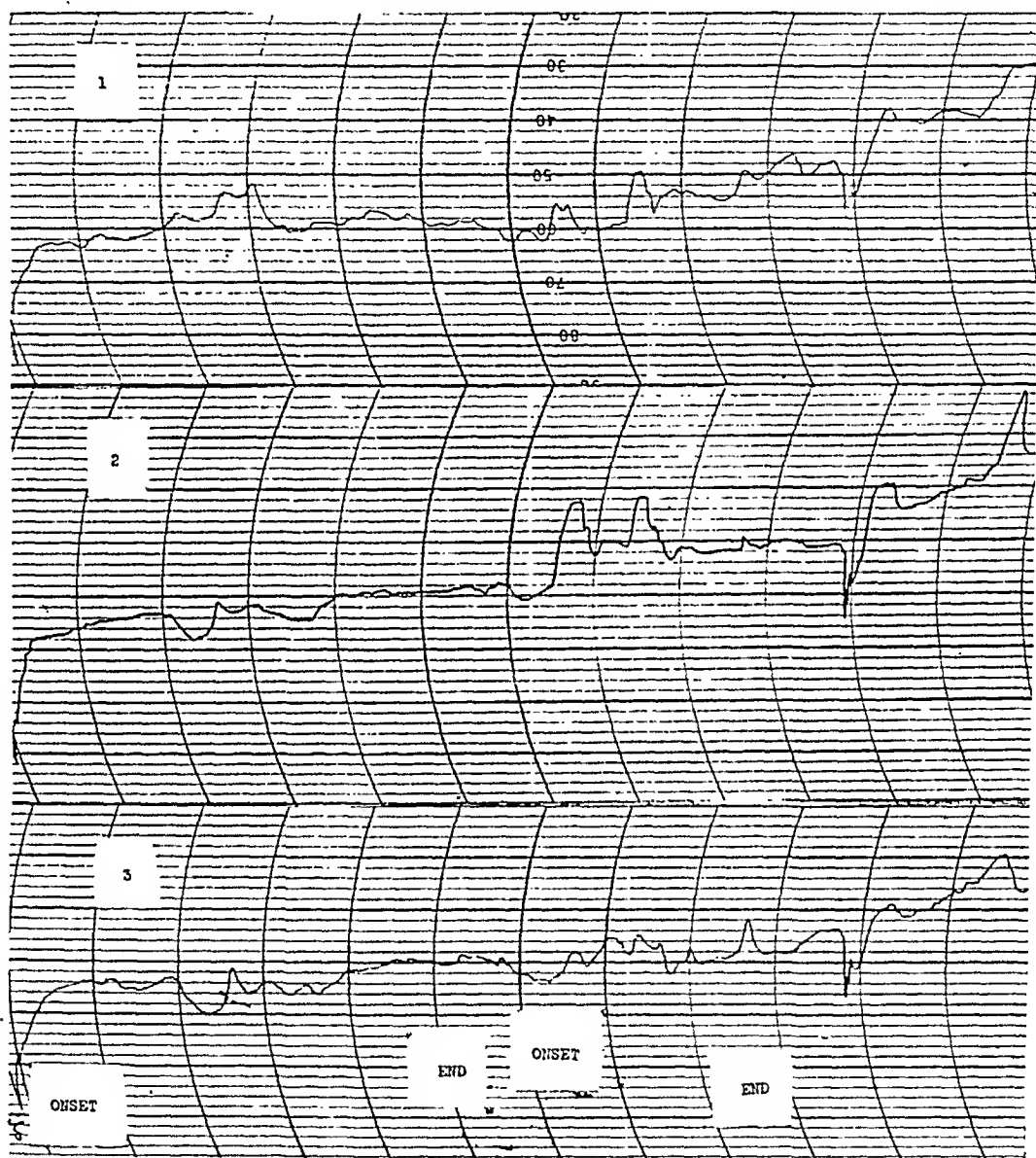


Fig. 6.—Strong labor. These curves are easily identified as coming from the same source. The trends, long period and short period variations are almost identical although variation in voltages of minor quality can be noted on comparison of leads.

Interpretation: In rapidly progressive labor, the changes in potential in all portions of the uterus are well coordinated and approximately identical. The basic potential of the uterine musculature under such circumstances is essentially the same in all areas.

Caudal Anesthesia

*Group I (Four patients).—*Very slowly progressive labor with contractions rendered entirely painless with caudal anesthesia.

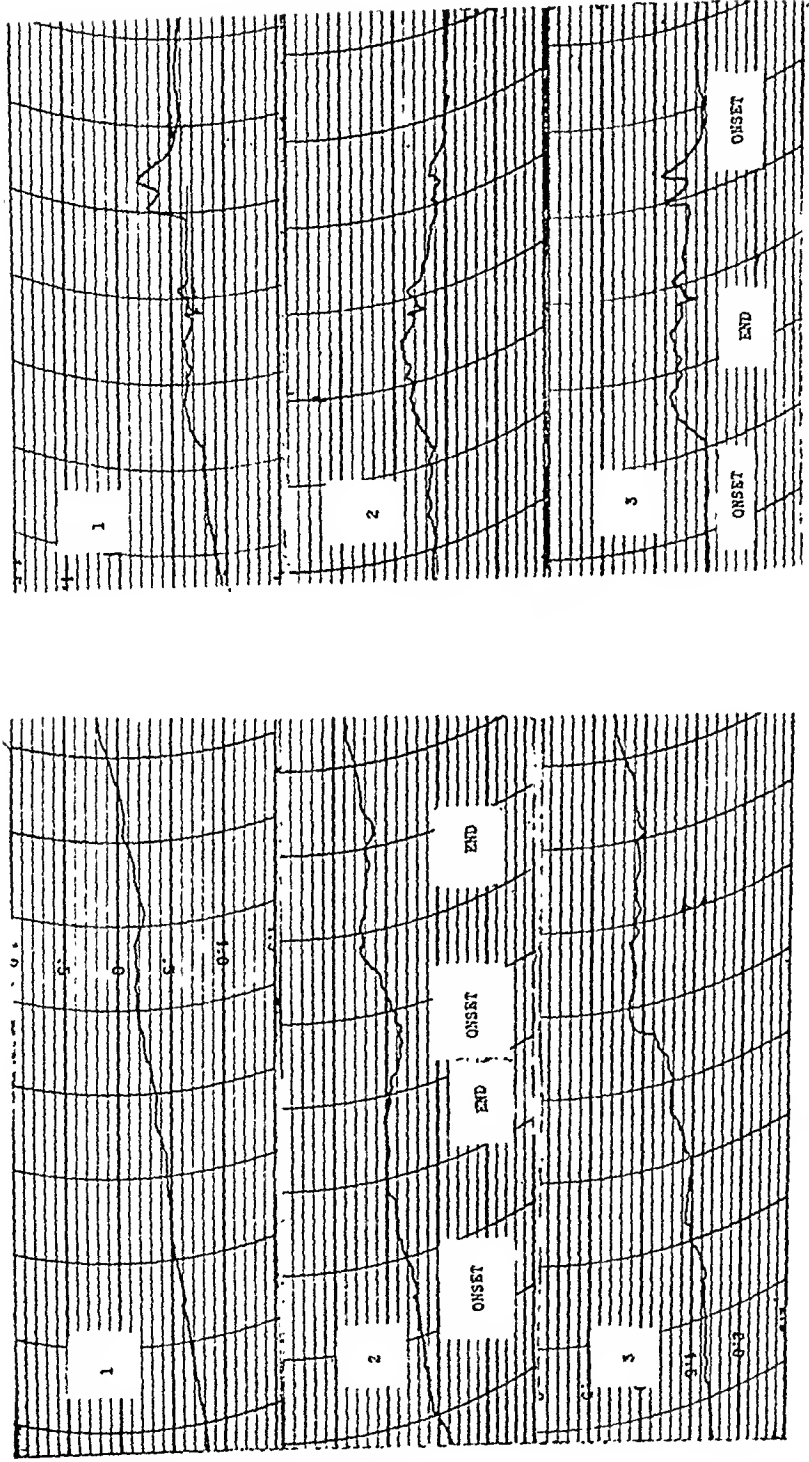


Fig. 8.

Fig. 9.

Fig. 8.—Moderate labor with slow progression with caudal anesthesia. The most striking feature noted is the lack of voltage in all leads. Trends are identical and although long and short period variations are dissimilar in phase and voltage, a general pattern can be recognized occasionally.

Fig. 9.—Progressive labor with caudal anesthesia. Although noticeable variation in voltage in the long and short period variations is present, the pattern of each lead is similar. The trend of Lead II, however, is out of phase as compared with Leads I and III. Pulse waves are frequent here and show significant amplitude.

Group II (Ten patients).—Progressive labor with painless contractions due to caudal anesthesia.

In general, with a satisfactory caudal anesthesia and moderate to severe labor, a definite pattern can be made out, and although all voltages are much lower than those noted in patients without this motor nerve block, there are definite variations. Fig. 9 demonstrates such a patient.

The pattern of each lead is recognizable as coming from the same source. The trends of Leads I and III are similar although Lead II is in inverse phase. In general, the short and long period variations are similar although differences of voltage of the same portion of the curve are obvious. In general, the short period variations are most marked in Lead II and the long period ones in Lead III. Pulse waves are identical in all leads. Fig. 10, demonstrating the recording from a patient in the same clinical type of good progressive labor, demonstrates that such similarity is not always evident. Here Leads I and III are relative in trend, although the amplitude of voltage change in Lead III is so large as to make the patterns seem quite unlike, and one complex found in the sample is entirely absent in both Leads I and II. Lead II, however, is entirely out of phase in the inverse direction when compared with Leads I and III with respect to trend, to long and short period variations, and even as to pulse waves.

Interpretation: Progressive labor made painless by means of caudal anesthesia is in general characterized by changes of potential of low voltage, but this voltage change is usually well coordinated and equally distributed over all areas of the uterus. In general, the severity of the contraction can be correlated with the amplitude of the change of potential. At times, single complexes may be completely out of phase and even the trends of voltage and the standing potentials may be quite different even in the presence of good labor. One complicating factor which cannot be completely evaluated at this time is the degree of effectiveness of the block to the motor impulses to the uterus. Figs. 11 and 12 demonstrate the effect on the recording of allowing the caudal to wear off partially so that the patient feels "pulling down" sensations with each contraction, and Fig. 12 shows that with repetition of the blocking drug there is a complete disappearance of these waves. This patient was able to obtain complete blockage of the impulses, or almost complete. Others have varying response, due no doubt to the degree and resistance of the nerve sheath. The possibility of completely evaluating this factor is of course remote.

Discussion

In our preliminary report¹ we were unable to evaluate (1) the part played by the contractions, visible or otherwise, of skeletal muscle; (2) individual variations due to technical errors inherent in the amplifying and recording apparatus; and (3) the apparent lack of uniformity of pattern associated with uterine activity. The large over-all effect of induction of caudal nerve block was noted and its effect in depressing large changes in voltages recorded.

With three electrodes spaced as described and a three-channel system for recording, we are able to elucidate certain of the phenomena and to speculate more accurately on other phases.

We feel that the part played by slight action of striated muscle in the recording is negligible, as can be inferred by (1) the failure of the instruments to be exactly synchronous at all times; (2) the absence of the same general pattern despite relatively severe motion; and (3) the difference in amplitude of one recorder as compared to the other two during a change in standing potential.

It is also reasonable to suppose that, unlike the heart, there is no general wave passage of constant pattern over the uterus, but merely relatively slow and very slow changes in potential which may occur in a localized area or which may be transmitted to all areas, rapidly and with no constant pathway.

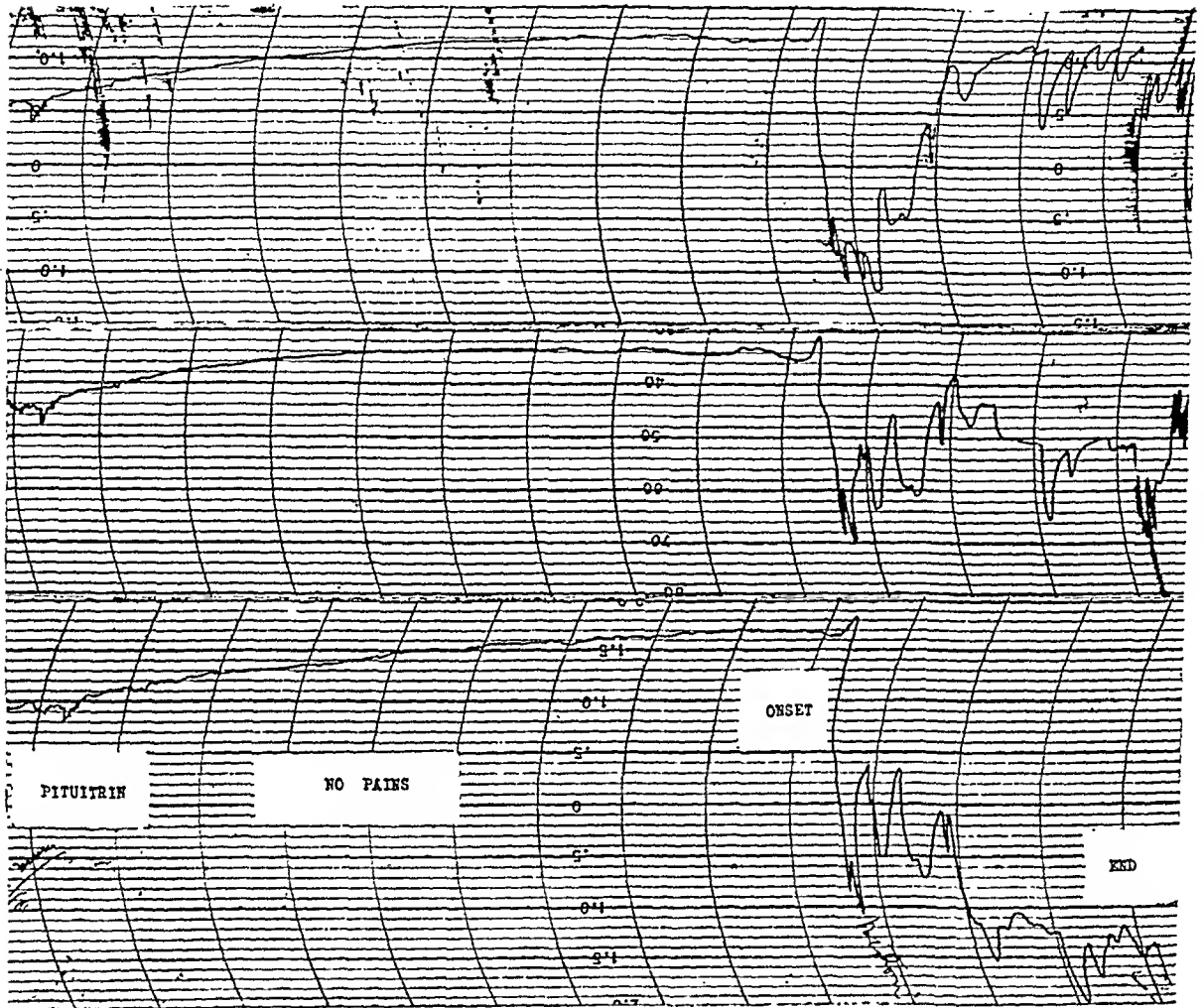


Fig. 13.—Labor depressed by heavy basal sedation, activated by Pituitrin. The changes in potential are minimal. There is almost complete disappearance of long and short period variations; the trend is in general similar. With the onset of Pituitrin action, there is an abrupt drop in potential in all leads, and the same relative pattern can be seen, although the trend of Lead I is upward, Lead III downward, and Lead II intermediate. Short and long period variations are in general similar.

The site of origin of these changes in potential is not constant; that is, there is no pacemaker. Rather, it seems likely, if our recorders are as synchronous as we believe, that the points of origin may be multiple and placed at any point on the uterine body, with the greatest frequency of origin in the lower portion of the uterus.

The cause of the change in pattern and voltage by the caudal nerve block can only be speculated upon, but it seems likely that by blocking these sensory nerve trunks we are also blocking parasympathetic nerve fibers which play a great part in the formation of the electrical pattern observed. This is inferred

MICROSCOPIC OBSERVATIONS OF THE PLACENTAL BARRIER IN TRANSPLACENTAL ERYTHROCYTOTOXIC ANEMIA (ERYTHROBLASTOSIS FETALIS) AND IN NORMAL PREGNANCY*

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MICROSCOPIC examination of the placentas of fifteen cases of erythroblastosis fetalis shows, in all, numerous breaks in the barrier associated with hemorrhage from the fetal circulation into the maternal intervillous spaces. In areas of very recent hemorrhage, nucleated red blood cells of the fetus are observed in the regional intervillous spaces. The breaks in the placental barrier involve the surface of villi and trunks and apparently result from the occlusion of peripheral capillaries or larger vessels by agglutinated red blood cells and fibrin. Regional to the areas of vascular occlusion, the overlying epithelium shows degenerative or necrotic change and, in places, erosion associated with hemorrhage from the fetal circulation into the regional intervillous spaces. Coincidentally, access of maternal blood to the fetal circulation is afforded. The mixture of bloods is stopped quickly, apparently, by the formation of a clot at the site of injury. In addition to these changes, the placentas of 8 of the 13 fatal cases show the thickened villi characteristic of the disease. In the 15 cases, the duration of the pregnancy was five months or more.

Microscopic examination of the placentas in 213 cases in the last half of normal pregnancy shows, in the barrier in all, numerous breaks of the same type as observed in the cases of erythroblastosis fetalis. In 130 cases in the first half of pregnancy, these changes are not observed until the third month, and then occasional villi only are seen involved. Toward the end of the first half of pregnancy, the number of involved villi and trunks increases.

In all these cases of erythroblastosis fetalis and of normal pregnancy, the blood clots associated with the erosions of villi and trunks are of variable size and shape. At times they are very small and cover the area of erosion only. Frequently however, especially when the vessels of trunks are involved, they extend for some distance and in all directions from their source. They bind villus to villus, villus to trunk, trunk to villus, and occasionally trunk to trunk. The recent clots appear soon to be molded, in great part, into shapes resembling portions of villi and trunks. The enmeshed cellular elements soon disappear and cylinders of fibrin remain. These are apparently quickly covered by syncytium growing from areas regional to the injury and from the villus, villi, or trunk to which they are adherent. Subsequently, connective tissue from regional structures grows into the fibrin cores and the completed structures are then indistinguishable from similar residual elements of the placenta.

*Received Sept. 18, 1947.

because of the complete loss in potential change by a highly effective caudal block and a gradual increase in amplitude of the waves noted on a less effective state of block. The alteration of pattern following a partially effective block of this sort is significant and noticeably different from that noted in patients without motor nerve interruption.

These findings suggest that motor impulses sent from the parasympathetic nervous system control normal uterine action but that, under conditions in which these impulses are blocked, an autonomous generation of contraction occurs.

The effect of sedation to the extent of cessation of contractions is associated with loss of electrical activity, and Pituitrin (probably acting directly on the smooth muscle and not on the nervous element) causes a resumption of electrical changes of potential. (Fig. 13.)

Conclusions

Changes in potential of low frequency associated with labor in the human uterus as recorded from the anterior abdominal wall by a three-channel system have been described.

Progressive labor is associated with over-all changes of potential of several millivolts of no definitely reduplicable pattern, path of conduction, or point of origin.

False labor, irregular painful contractions of the uterus associated with slowly progressive dilatation of the cervix, is usually characterized by changes of potential of low voltage which differ in various areas of the musculature and demonstrate no general correlated effect.

True labor, characterized by regular rhythmic contractions and progressive dilatation of the cervix, is usually associated with changes of potential of high amplitude, synchronous in all leads.

Contractions are associated in general with a higher standing voltage and possibly slightly less activity than are the "between contractions" periods.

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of erythrophagocytosis in the disease is the autopsy finding, in a 33/4-month-old infant in a case of B,O and RH, rh incompatibility, of an enormous number of macrophages with engulfed red blood cells in the spleen, lymph nodes and bone marrow especially. The term "congenital hemolytic anemia," therefore, is not entirely accurate and "transplacental erythrocytotoxic anemia" is suggested as a better name for the disease.

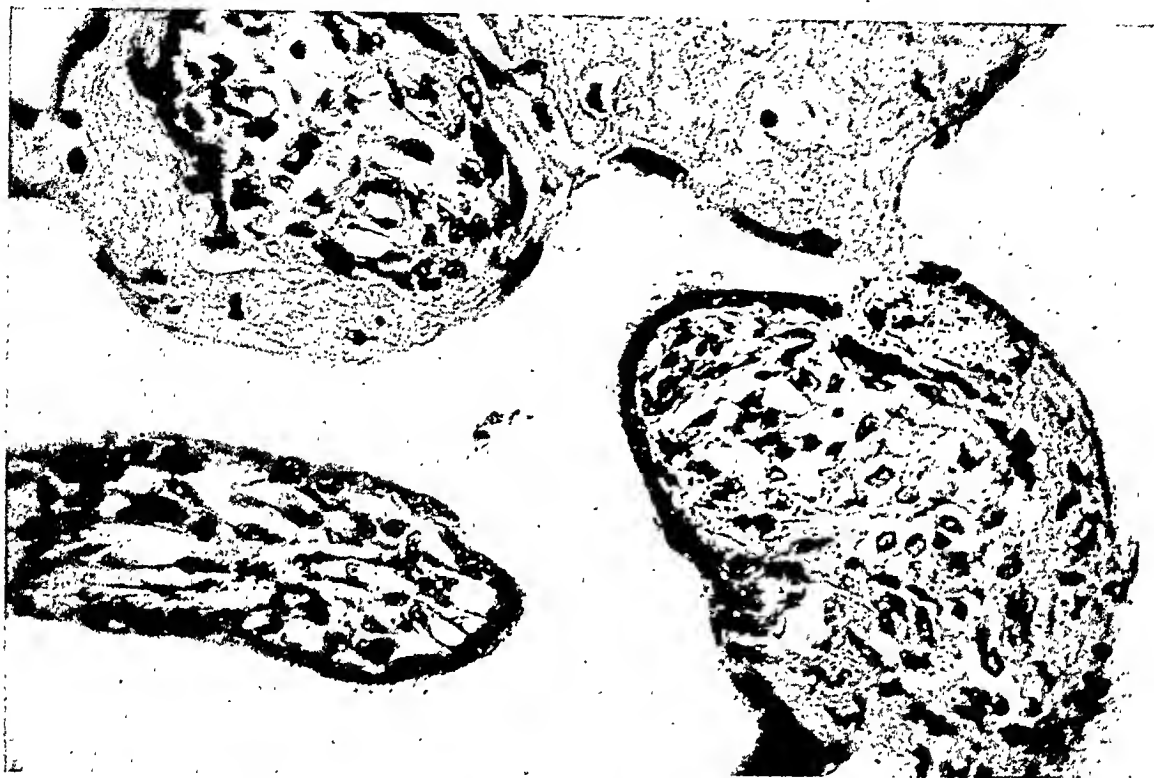


Fig. 2.—Villi of six months' normal pregnancy. (High magnification.) Erosions epithelium, hemorrhage, blood clot formation in intervillous spaces with adhesion of villi.

Placenta of Transplacental Erythrocytotoxic Anemia (Erythroblastosis Fetalis)

The placentas of 15 cases of transplacental erythrocytotoxic anemia (erythroblastosis fetalis) (13 from fatal cases and 2 from cases of recovery after treatment) when received in the department were examined grossly and representative blocks of tissue about 1 1/2 cm. by 1 cm. by 1/2 cm. were cut and fixed in neutral 10 per cent formalin. Sections 8 to 10 microns thick were cut from the paraffin-embedded blocks and stained with hematoxylin and eosin.

Microscopic examination of the sections shows, in all 15 placentas, numerous breaks in the placental barrier involving the surface of villi and trunks with hemorrhage from the fetal circulation into the maternal intervillous spaces. In areas of very recent hemorrhage, nucleated red blood cells of the fetus are observed in the regional intervillous spaces. Throughout the sections, numerous villi and trunks show degeneration, necrosis, and erosion of epithelium. Associ-

The demonstration of numerous breaks in the placental barrier in the cases of erythroblastosis fetalis in the last half of pregnancy adds evidence confirming the fundamental studies of Levine,¹ which firmly established erythroblastosis fetalis as a disease caused by the destruction of fetal red blood cells by antibodies produced in the mother to some incompatible factor which the fetal red blood cells contain. The types of factors involved in the disorder have been greatly clarified by the studies of Landsteiner and Wiener,² Wiener,² Levine,¹ and their associates.



Fig. 1.—Villus of full-term normal pregnancy. (Very high magnification.) Vascular occlusion by agglutinated RBCs, degeneration and necrosis of regional epithelium.

The study of the placental barrier in erythroblastosis fetalis here reported also corroborates the occasional formation in the placenta of such cases, of hematomas containing nucleated fetal red blood cells as first reported by Javert.³

Since it is now known that the erythroblastosis in the disease is a secondary manifestation, the designation "erythroblastosis fetalis" is no longer justified. Furthermore, it has been found that destruction of the incompatible fetal red blood cells in the disease occurs in part by phagocytosis.⁴⁻⁷ Additional evidence

TABLE I. FIFTEEN CASES OF TRANSPLACENTAL ERYTH

| AUTOPSY NUMBER | AGE BABY LUNAR MONTHS | BABY WEIGHT | PLACENTA WEIGHT | RATIO PLA- CENTA BABY | BABY LIVED | BABY STILL BORN | BABY MAC- ER- ATED | GROSS ABNORMALITY PLACENTA |
|----------------------------------|--------------------------------|----------------|----------------------------------|--------------------------------|---------------|-----------------------|-----------------------------|--|
| 1114 | F.T. | 4400 | No ab. | | | X | | None |
| 1130 | F.T. | 3320 | 26x14x3 cm. | | | X | | Large |
| 1451 | 8 | 1500 | Larger thicker than normal | | | X | | Large thicker than normal ? |
| 1979 (a) | 8½ | cr 31 | | | 33 min. | | | |
| 2090 (b) | F.T. | 2730 | | | | X | X† | ? |
| 2091 (a) | 5 | 380 | 15x12x2.5 | | | X | X† | Coarse |
| 2101 | 8½ | 2700 | 900 | 1:3 | | X | | Large, coarse |
| 2134 (c) | F.T. | 4200 | 750 | 1:5.6 | | X | X slight | No abnormality |
| 2165 | 6 | 425 | 125 | 1:3.4 | | X | X† | Large, boggy |
| 2169 | 9 | 2150 | 350 | 1:6.1 | | X | X† | No abnormality |
| 2186 | 5½ | cr 18 | 96 | | | X | X | No abnormality |
| 2243 | 7½ | 1740 | 1640 | 1:1.1 | 25 min. | | | Very large, coarse some hydatid cysts |
| 2330 (b) Surgical Path. | 9 | 2840 | 1260 | 1:2.3 | | X | | Over twice normal size, coarse |
| 53424 (c) | F.T. | 3220 | | | A and W | | | |
| 53833 | F.T. | 3270 | | 1:5.1 | A and W | | | |

(a) (a) - (b) (b) - (c) (c) = Siblings.

*Including focal masses of necrotic epithelium as in early normal pregnancy; some nucleated red blood cells in intervillous spaces.

†Including several hematomas over 1 mm. in diameter, scattered recent hemorrhage from fetal villi with nucleated red blood cells in intervillous spaces.

and trunks show degenerative changes and shrinkage, in places complete obliteration. Some show thickened endothelium and prominent perivascular fibrosis. Of the five remaining cases, the villi in four placentas show generalized degenerative changes with blood vessels collapsed, the picture that of retained placenta (dead fetus). In one placenta, in a case of a first born child with transplacental erythrocytotoxic anemia (erythroblastosis fetalis) of full term pregnancy, about 20 per cent of the villi are edematous, and show degenerative changes of central vessels. The epithelium, however, is not thickened and the villi are not characteristically those of transplacental erythrocytotoxic anemia (erythroblastosis fetalis). The placentas of the two cases that recovered from the disease show no abnormalities whatever of villi and trunks.

Table I presents data relating especially to the placental findings of the 15 cases. A full report, including gross and microscopic observations of the organs of the stillborn and newborn babies, will be published later.

Placenta of Normal Pregnancy

In contrast to placental to baby ratios of 1:6.1 to 1:1.1 in cases of transplacental erythrocytotoxic anemia (erythroblastosis fetalis), ratios of 1:12 to

ated with the erosions there are recent or old blood clots. The lesions are apparently due to the occlusion of regional peripheral capillaries by agglutinated red blood cells and fibrin. The blood clots continue from damaged villus or trunk to regional villus, villi, or trunk. In the majority of clots, the cellular elements are no longer visible and the masses appear as cylinders of fibrin conforming to the shape of the intervillous space or spaces and resemble shorter or longer branches of villi or small trunks. The newly formed structures are soon covered by syncytium growing from that region to the areas of erosion. Later changes of ingrowth of connective tissue from involved villus, villi, or trunks are

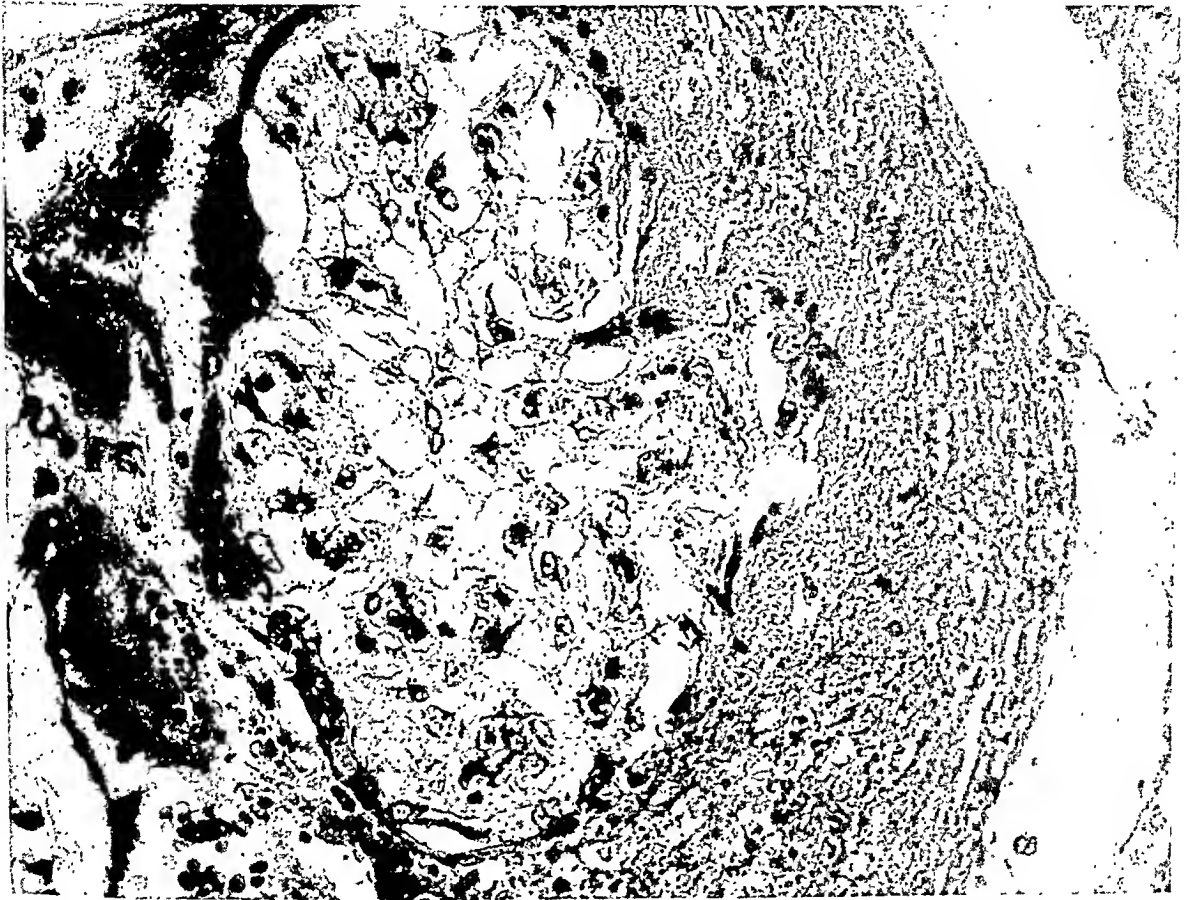


Fig. 3.—Villus of eight and one-half months' pregnancy, case of erythroblastosis fetalis. (High magnification.) Erosion epithelium, hemorrhage into regional intervillous spaces with early clot formation. (Numerous nucleated RBCs lower left.)

observed and eventually complete fibrovaseular anastomosis of these structures is seen. Although it is possible to recognize newly forming villuslike and trunklike structures on the scaffolding of the fibrin of fetal blood clots, it is impossible to tell recently completed structures from branches of residual villi or portions of residual trunks. In one of the placentas, several hematomas 1 mm. to 4 mm. in diameter are observed and in places, enmeshed in the fibrin, nucleated red blood cells are present.

In 8 of the 13 fatal cases, the villi show the changes characteristic of the disease,⁸ many are much thicker than normal and some are edematous. The surface epithelium is thickened and in places double. The stroma is thicker than average and compact where not edematous. Many of the central vessels of villi

The average ratio was 1:6.4, the lowest ratio was 1:4, the highest 1:12.

Coincident with the study of the placenta in transplacental erythrocytotoxic anemia (erythroblastosis fetalis), microscopic examination was made of the placenta of normal pregnancy. As in the case of the 15 placentas described above, the normal placentas received in the department in the past 18 years were examined grossly and representative blocks of tissue about $1\frac{1}{2}$ cm. by 1 cm. by $\frac{1}{2}$ cm. were cut and fixed in neutral 10 per cent formalin. Sections 8 to 10 microns were cut from the paraffin-embedded blocks and stained with hematoxylin and eosin. The placentas studied were as shown in Table II.

TABLE II. PLACENTAS EXAMINED

| | | LUNAR MONTHS | | | | | |
|--------------------------|---------------------|--------------|----------------|----------------|----------------|-----------------|-------|
| | | 0-2 | OVER 2 TO 4 | OVER 4 TO 6 | OVER 6 TO 8 | OVER 8 TO 10 | TOTAL |
| Normal | In situ in utero | 3 | 44 | 8 | 1 | 5 | 61 |
| Normal | Not in situ | 0 | 70 | 15 | 4 | 193 | 282 |
| Normal | Total | 3 | 114 | 23 | 5 | 198 | 343 |
| Inflamed | | | | | | | 8 |
| Erythroblastosis fetalis | | | | 3 | 2 | 10 | 15 |
| Grand Total | | | | | | | 366 |

Placenta of Very Early Pregnancy (0 to 2 Lunar Months)

Microscopic examination of an intact and well-fixed specimen of about two weeks' pregnancy ($3\frac{1}{2}$ mm. in diameter) and a second specimen of about three weeks' pregnancy (17 mm. by 6 mm. in diameter) both in situ in utero, show the structures described in the standard textbooks of embryology⁹ and obstetrics.¹⁰ The villi and central trunk show no degenerative changes of epithelium or stroma. Sections show clearly the vigorous dissection of the maternal decidua by large syncytial cells adjoining one another or spearheading the tips of growing villi. The sections, furthermore, show invading syncytial cells opening up blood vessels of the regional maternal tissues and the dissection of the decidua into many villuslike cylinders. To the ends and sides of these structures the tips of chorionic villi are firmly bound by syncytial cells (fastening villi). Examination of the villi of a pregnancy of about one and one-half months shows no appreciable changes of epithelium or stroma.

Placenta of Over Two Months' to Four Months' Pregnancy

Microscopic examination of 114 placentas of over two months to four months shows the majority of villi to be about 150 to 200 microns in thickness at two months, about 300 microns at three months, and about 400 microns at 4 months. Syncytial and Langhans layers are both present until toward the end of this period, when Langhans cells are fewer than previously. The fibrous tissue core at four months is decidedly thicker than previously, but the cells are still of early fibroblastic type. Blood vessels appear most prominently in the placentas of the third month, many lying just below the epithelium, and are filled with nucleated red blood cells. The vessels in small and large villous trunks, especially the latter, are identifiable as arteries, veins, and capillaries. In some of the sections, small hemorrhages within occasional villi are observed, and Hofbauer cells are seen fairly frequently, especially in placentas of about four months' pregnancy. Some contain altered red blood cells. Early in the period,

ROCYTOTOXIC ANEMIA (ERYTHROBLASTOSIS FETALIS)

| FIBROUS VILLI TYPICAL OF TEA (EF) | | VILLI NOT TYPICAL OF TEA (EF) PER CENT VILLI AND TRUNKS | EROSION CLOTS PER CENT VILLI AND TRUNKS | | | MOTHER BLOOD TYPE | MOTHER RH ANTI- BODY | BABY BLOOD TYPE | FATHER BLOOD TYPE |
|--------------------------------------|--|--|--|------|------|-------------------------|-------------------------------|-----------------------|-------------------------|
| PER CENT VILLI AND TRUNKS | WITH EDEMA PER CENT VILLI AND TRUNKS | | | PARA | GRAV | | | | |
| 10 | 0 | 90 | 30 | 2 | | | | | |
| 20 | 40 | 40 | | 1 | 3 | | | | |
| 60 | 30 | 10 | 25* | 1 | 3 | | | | |
| 40 | 50 | 10 | 30† | 1 | 2 | rh, A | high dilution | RH | RH, O |
| ? | ? | ? | 20 | 1 | 2 | rh, AB | | | RH, B |
| ? | ? | ? | 35 | 2 | 3 | rh, A | | | RH, O |
| 25 | 50 | 25 | 20 | 1 | 2 | rh, A | undiluted serum | RH | RH, O |
| 0 | 0 | 80 like 7-8 mo. 20 with edema | 12 | 0 | 1 | rh, A | | | RH, B |
| 0 | ? | 100 slightly thicker | 40 | 1 | 4 | rh, A | 1:16 | | RH, A |
| 0 | ? | 100 10% thicker than average | 30 | 1 | 3 | rh, AB | 1:64 | | RH |
| ? | ? | ? | ? | 1 | 3 | rh, A | 0 | | |
| 20 | 60 | 20 | 30 | 1 | 2 | rh, A | 0 | RH | RH |
| 20 | 65 | 15 | 12 | 1 | 3 | rh, AB | agg—1:64 cong—1:128 | | RH, B |
| 0 | 0 | 100 | 12 | 1 | 2 | rh, A | | RH | RH |
| 0 | 0 | 100 20 with edema | 20 | 1 | | rh | agg—undil cong—1:32 | RH | |

†Retained placenta with degenerative changes (fetus long dead).

F.T.=full term.

TEA (EF) = transplacental erythrocytotoxic anemia (erythroblastosis fetalis).

A and W=alive and well.

1:4 were found in a series of 493 consecutive full-term normal deliveries at the hospital from Nov. 2, 1946, to Feb. 27, 1947. The ratios and the percentages* are as follows:

| RATIO | NUMBER OF NORMAL PLACENTAS | PERCENTAGE |
|---------|----------------------------|------------|
| 1 to 4 | 17 | 3.4 |
| 1 to 5 | 88 | 17.8 |
| 1 to 6 | 180 | 36.5 |
| 1 to 7 | 133 | 26.9 |
| 1 to 8 | 48 | 9.7 |
| 1 to 9 | 21 | 4.2 |
| 1 to 10 | 4 | 0.8 |
| 1 to 11 | 0 | -- |
| 1 to 12 | 2 | 0.4 |
| Total | 493 | |

*Dr. A. M. Young kindly obtained the information and made these calculations.

finally, erosion of regional epithelium, regional hemorrhage of fetal blood into the maternal circulation in the intervillous spaces, recent or older regional blood clot continuing from damaged villus or trunk to regional villus, villi or trunk. In the majority of clots, the cellular elements are no longer visible and the masses appear as cylinders of fibrin. In a few placentas, earlier changes are observed and red blood cells enmeshed in the fibrin are easily identifiable. In the placentas with early changes following focal vascular occlusion, the adherent clots are irregular in shape. Subsequently they appear molded to conform to the intervillous space or spaces and consist in great part of fibrin. These fibrin masses, resembling in shape shorter or longer branches of villi or small trunks, are apparently soon covered by syncytium growing from areas regional to the eroded epithelium. At times, especially with involvement of larger vessels of small trunks, the hemorrhages are larger and the resultant fibrin is observed intimately encircling a number of villi, the latter showing degenerative or necrotic change. Later changes of ingrowth of connective tissue from involved villus, villi, or trunks are observed, and eventually complete fibrovascular anastomosis of these structures is seen. Although it is possible to recognize newly forming villuslike and trunklike structures on the scaffolding of the fibrin of fetal blood clots, it is impossible to tell recently completed structures from branches of residual villi or portions of residual trunks. In some placentas at this time, many of the masses of fibrin, progressively replaced by connective tissue ingrowth, show the newly formed cells to be decidedly larger than the residual connective tissue cells from which they spring. At times these fetal cells are indistinguishable from decidual cells. (It should be recalled that not infrequently a distant decidual reaction occurs in cases of uterine pregnancy and recently formed fibrous tags replacing blood clots adherent to the surface of the ovary, omentum, appendix, etc., show some connective tissue cells transformed into typical decidual cells.) The picture in the placentas of this and later periods suggests that newly formed fetal connective tissue cells growing into fetal blood clots in intervillous spaces and exposed to the progesterone in the maternal circulation, respond to it just as the endometrial stromal cells and newly formed maternal connective tissue cells elsewhere do. Since the placentas of all ages contain well-defined decidual septa, it is difficult to distinguish areas of organizing fetal clots from islands of maternal decidual cells.

Placenta of Over Six Months' to Eight Months' Pregnancy

Microscopic observation of five placentas of this period show villi somewhat thinner than previously. The blood vessels are more numerous and the stroma more compact than before. The syncytial cells are thinner than they are earlier and there is less fibrous stroma between them and the vascular endothelium. As in the placentas of the fifth and sixth month, numerous focal areas of occlusion of peripheral vessels of villi and trunks by agglutinated red blood cells and fibrin are seen. Associated therewith, the regional epithelium shows degenerative and necrotic change and in places, erosion. Adherent to the sites of injury, recent or old blood clots are observed. Many continue from damaged villus or trunk to regional villus, villi, or trunk. Likewise, the later changes of organization noted in placentas of the previous period are observed. As before, complete anastomosis of villus with villus, villus with trunk, and trunk with trunk is observed, and somewhat more frequently than earlier. Similarly, areas of organizing fetal clots resembling islands of maternal decidual cells are seen. These areas vary from a few hundred microns to over 4 mm. in diameter. Some show ingrowth of blood vessels, others show degenerative or necrotic change of some of the large cells.

the syncytial cells vary in size and are very large at the tips of some of the villi. In the placentas of the second month, occasional villi are observed showing degenerative changes of the epithelium, especially of the syncytium: vacuoles of varying size, cells shrunken, nuclei pyknotic or eosin-stained, cytoplasm granular and intensely stained. Villi and villous trunks show adherent focal masses of degenerated epithelium. These changes are observed as early as about the end of the second month and with increasing frequency toward the fourth month. As early as the third month, occasional villi are observed loosely adherent to each other by masses of degenerated epithelium, more rarely by a recent or older blood clot regional to an area of erosion associated with a peripheral vessel occluded by agglutinated red blood cells and fibrin.

The picture of villi with vascular occlusion and regional epithelial degeneration, necrosis, erosion and hemorrhage is not unlike that of vascular occlusion, tissue necrosis, disintegration, and hemorrhage of the endometrium in the menstrual phase.

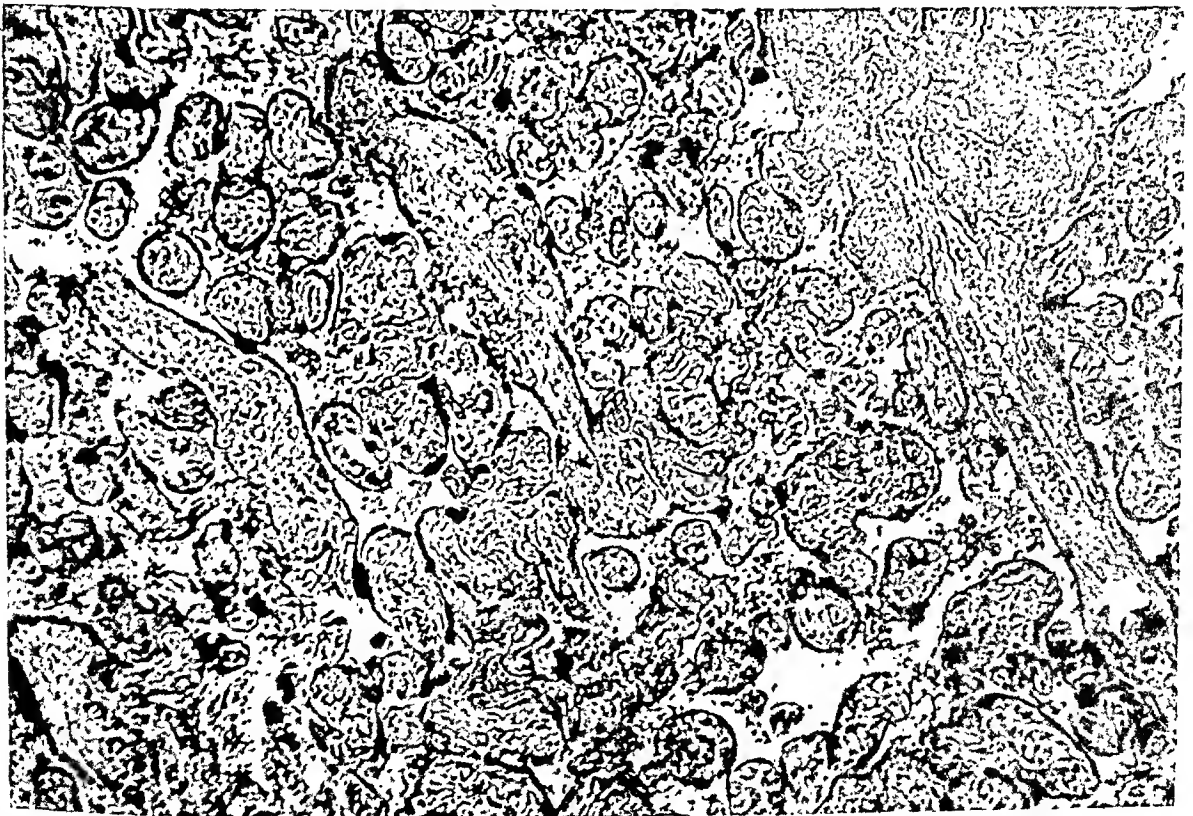


Fig. 4.—Villi and trunks of full-term normal placenta. (Low magnification.) Many with epithelial erosion and adherent blood clot.

Placenta of Over Four Months' to Six Months' Pregnancy

Microscopic examination of 23 placentas in this period show villi progressively thinner than previously and with stroma more compact. The Langhans cells are few in number or completely absent, syncytial cells thinner than at earlier periods. Villi with adherent masses of degenerated epithelium are less frequent than in earlier months; but now many villi and trunks, especially in the placentas of the fifth and sixth month, show focal areas of occlusion of peripheral capillaries by agglutinated red blood cells and fibrin, necrosis, and,

Summary

Microscopic examination of the placentas of fifteen cases of erythroblastosis fetalis shows, in all, numerous breaks in the barrier associated with hemorrhage from the fetal circulation into the maternal intervillous spaces. In areas of very recent hemorrhage, nucleated red blood cells of the fetus are observed in the regional intervillous spaces. The breaks in the placental barrier involve the surface of villi and trunks and apparently result from the occlusion of peripheral capillaries or larger vessels by agglutinated red blood cells and fibrin. Regional to the areas of vascular occlusion, the overlying epithelium shows degenerative or necrotic change and in places erosion associated with hemorrhage from the fetal circulation into the regional intervillous spaces. Coincidentally, access of maternal blood to the fetal circulation is afforded. The mixture of bloods is stopped quickly, apparently by the formation of a clot at the site of injury.

Since it is now known that the erythroblastosis in the disease is a secondary manifestation, the designation "erythroblastosis fetalis" is no longer justified. Furthermore it has been found that destruction of the incompatible fetal red blood cells in the disease occurs in part by phagocytosis. The term "congenital hemolytic anemia," therefore, is not entirely accurate and "transplacental erythrocytotoxic anemia" is suggested as a better name for the disease.

Microscopic examination of the placentas in 213 cases in the last half of normal pregnancy shows, in the barrier in all, numerous breaks of the same type as observed in the cases of erythroblastosis fetalis.

In all these cases of erythroblastosis fetalis and of normal pregnancy, the blood clots associated with the erosions of villi and trunks are of variable size and shape. At times they are very small and cover the area of erosion only. Frequently, however, especially when the vessels of trunks are involved, they extend for some distance and in all directions from their source. They bind villus to villus, villus to trunk, trunk to villus, and occasionally trunk to trunk. The recent clots appear soon to be molded, in great part, into shapes resembling portions of villi and trunks. The enmeshed cellular elements soon disappear and cylinders of fibrin remain. These are apparently quickly covered by syncytium growing from areas regional to the injury and from the villus, villi, or trunk to which they are adherent. Subsequently, connective tissue from regional structures grows into the fibrin cores and the completed structures are then indistinguishable from similar residual elements of the placenta.

I wish to acknowledge with thanks the helpful suggestions concerning the manuscript of Drs. A. M. Young and J. M. Levin and their kindness in facilitating the examination of the slides. I wish also to thank Miss Josephine Jones for her preparation of the excellent sections examined and Mr. William Stevenson for the excellent photographs he made for the manuscript.

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Placenta of Over Eight Months' to Ten Months' Pregnancy

Microscopic observations of placentas of this terminal period show villi still thinner than previously and with blood vessels still more numerous and more prominent than earlier. The fibrous stroma between syncytium and vascular endothelium is comparatively small in amount and compact. As in placentas of the previous period, areas of vascular occlusion, regional epithelial necrosis and erosion associated with hemorrhage of fetal blood into the regional intervillous spaces is observed. Numerous villi and trunks show adhesion by recent and old clots and many show partial to complete organization with anastomosis of villus to villus, villus to trunk, and trunk to trunk. Islands of fetal connective tissue cells resembling decidual cells are present, some show areas of degeneration and necrosis and some show calcific deposits. Other well-known changes of maturation and senescence of the placenta are clearly visible in the terminal period.



Fig. 5.—Portion of placenta of eight and one-half months, case of erythroblastosis fetalis. (Low magnification.) Epithelial erosions villi and trunk, regional recent hematoma. (Scattered nucleated RBCs present.)

The observations of the 343 normal placentas are in keeping with those of Stieve,^{11, 12} who found adhesion of many villi as early as the fourth month and massive adhesion and anastomosis in the second half of pregnancy, with the placenta resembling a sponge in structure rather than a thicket of miniature trees, each tree independent of its neighbor, as previously believed.

Patten, remarking on the multiplicity and complexity of the structural units composing the human placenta, aptly stated that they were all "tangled together with no consideration for the microscopist."

PROGRESSIVE RESISTANCE EXERCISE IN THE FUNCTIONAL RESTORATION OF THE PERINEAL MUSCLES

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INTENSIVE investigations and experiences of World War II, the recent studies of physiologists, and research in infantile paralysis have greatly changed the methods of conserving and restoring skeletal muscle function. This knowledge has not been applied to genital relaxation to appreciable extent.

A restudy of the problems of the lax perineum in relation to modern concepts of muscle-cell regeneration and function reveals that birth-canal musculature is especially responsive to an improved method of conserving and restoring function.

The process of childbearing, although ordinarily considered a normal physiologic function, is invariably attended by a certain amount of injury to the tissues of the uterus, cervix, vagina, and perineum. In the majority of women, healing takes place rapidly and the structures are quickly restored to a state which makes a repetition of the process possible. Never, however, do the organs resume their original integrity of form and function.

Modern advances in obstetrics have led to a great reduction in the loss of life associated with childbearing. Infection, hemorrhage, and toxemia, the three principal causes of death in the parturient woman, claim fewer lives every year, and toward the accomplishment of this end obstetric research has been largely directed.

It is not enough, however, merely to keep a woman alive; it is important to preserve for her the function of her reproductive system and to prevent injury so far as possible, in order that the involved organs may again approximate a normal state. Although some injury is inevitable, the manner in which labor and delivery are conducted and the way in which the patient is cared for in the postpartum state will in large measure determine the extent and permanency of that injury.

Mechanism of Injury

The delivery of a child is possible because the uterine and abdominal muscles can exert a force great enough to overcome the resistance of the birth canal. An object approximately 10 cm. in diameter is gradually pushed through the cervix, which has an initial opening of only a few millimeters, and through the vagina, with its lumen of only a few centimeters. Changes take place during the course of pregnancy which prepare these structures for the dilatation which is necessary before the child can be delivered. The tissues become progressively softer and more elastic, and, by the end of pregnancy, the cervix is usually so altered that it becomes completely effaced and dilated and permits the passage of the infant without undue strain.

The muscles of the perineum are less adequately prepared, and when the presenting part of the infant is forced into the vagina and against the perineal

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and resilient and is capable of undergoing a greater change than any other part of the perineum. Muscles in this area are injured to some extent in every pregnancy but in most instances show amazing recuperative powers.

When muscles and fascias are subjected to excessive tension during childbirth, two types of injury may result: (1) actual laceration and separation of the muscles and fascias and (2) separation of individual muscle cells from the motor nerves by which they are innervated. The latter injury is probably universal, owing to the great elasticity of muscle cells and the relatively lesser tensions which nerve fibers can withstand.

With the birth of the baby, the force which has been applied to the perineum suddenly ceases. The muscles and fascias of the peripheral zone, which have been subjected to proportionately less tension stress than those of the medial zone, contract, to cause reduction in the circumference, shape, and form of the vagina. In this position they serve as supportive splints for the medial muscles and fascias, which were the site of the most concentrated tension stress. Contraction occurs gradually, for a state of tension is never conducive to rapid healing, and only after some time does the vagina approximate its former size and the perineum approach its original competency.

The forces which lead to the dilatation of the birth canal and the consequent stretching and tearing of muscle and nerve fibers vary in their nature and in their effect on the perineal structures. The relative size of the fetal head and the bony pelvis, the position the head assumes in the pelvis, the character of the uterine contractions, the length of time during which force is exerted and the state of the perineal muscles, all play a part in determining the extent to which the perineum will be injured. In a young woman with resilient, elastic muscles, if the head is in an occipitoanterior position, the uterine contractions are normal, and an episiotomy has been done to prevent overdistention of the perineum, permanent injury is minimized.

In any region where tissues become overstretched, even though lacerations of muscles or fascias are not visible, nerve injury is inevitable. Every muscle cell is supplied with a motor end-plate, attached to one of the many filaments making up the terminal portion of a motor nerve. Since muscle cells are capable of greater extension than nerve fibers, they may stretch to such an extent that the motor end-plates are torn from the nerves of which they were a part. Never are all such connections severed. Some muscle cells will retain their innervation and be capable of acting as splints or crutches for their injured neighbors. The amount of permanent muscle relaxation will depend in large measure on the proportionate numbers of intact and disrupted nerve-muscle units and the number which are reconstructed.

Mechanism of Reconstruction

It is not enough, therefore, to approximate the margins of lacerated muscles and fascias and suture them in place. Such a procedure will ordinarily lead to a restoration of the gross form of the perineal structures but will not in itself bring about a return to normal function. In some way, re-innervation of muscle cells must be accomplished and the injured muscle cells must again be educated to function.

The situation most favorable for a return of function is a demand for use. Fiseher⁵ stated that in general an inactive injured muscle will lose almost 80 per cent of its weight, while an active injured muscle will lose only 20 per cent. Injured perineal muscle cells are in an ideal situation for maintenance of size through activity. The interspersed intact muscle cells are ordinarily sufficiently

muscles, less dilatation occurs. Instead, as the lumen of the vagina increases in diameter, the cells in those portions of the radially inserted muscles which lie nearest the vaginal orifice become separated from each other as a result of lateral stretching, while the interdigitating muscles which surround the vagina are often torn as a result of overelongation.

When any large object is forced against a diaphragm with a smaller opening, the greatest stress is at the margin of the orifice. The more peripheral areas are subject to much less strain, and it is the area immediately adjacent to the opening which becomes excessively stretched or torn. This is true of the perineum during childbirth. It is in close proximity to the vagina that the most severe injuries occur. Only after the medial tissues have given way do the peripheral zones become involved.

As the perimeter of the birth canal expands during delivery and approaches the fixed rim of the pelvis, the musculofascial tissues situated radially between the vagina and the rim of the pelvis would become shortened and relaxed if the expanding movement were entirely linear. If the tissues remained in the original plane, the medial fibers of the radially inserted muscles would be pulled apart and separated, but the muscles would never be subjected to excessive longitudinal tension.

To illustrate this process, one may picture the pelvis as a hoop 12 cm. in diameter; attached to it by means of rubber bands 5 cm. long is a small centrally placed hoop 2 cm. in diameter, which represents the undilated vagina. The rubber bands hold the two hoops in one plane. If, now, the diameter of the inner hoop is increased to 10 cm. to correspond to the dilatation necessary to permit passage of the child's head and the two are still held on the same plane, the rubber bands are each 4 cm. longer than necessary to keep the two hoops attached. It is thus evident that the inner hoop may move from the plane of the outer hoop 4.89 cm. without tension. Only when the perineum is forced outward more than the amount permitted by the elasticity of the tissues will injury be inflicted, and it is at approximately this point that an episiotomy is often performed in order to increase the diameter of the vaginal outlet and prevent further downward pull on the musculofascial tissues.

Variations in anatomic relations may be responsible for differences in the tension to which the muscles in any quadrant are exposed. Short anterior muscles may be subjected to excessive tension, leading to injury of the anterior vaginal wall. Posterior muscles are more commonly overextended by the descending head and are more commonly injured. Excessive tension in a quadrant of one diameter will cause relaxation of muscles in both quadrants of the opposite diameter. For this reason lateral muscles are rarely injured.

Other muscles and fascias which are intimately concerned with the support of the pelvic structures and which must become dilated to permit the passage of the infant are the sphincters which surround the anus and vagina. Curtis and his associates¹ have shown that strands of muscles which are predominantly for support blend with and insert themselves by interdigitation into the intrinsic musculature of the lower third of the vagina as well as that of the urethra and anus. Gorsch² has emphasized that "the deep muscular strata, which consist of the levator ani together with its fascia, are more or less closely interrelated with the perineal sphincters. By supporting and fixing the pelvic diaphragm the levators synergize and coordinate the activity of the sphincters." According to Hill and van Del,³ "the levator ani muscle acts as a powerful sphincter, since it surrounds the vagina like a loop," and Burch⁴ has made the statement that "relaxation of the vaginal outlet is caused by a lack of tone of the levator ani muscle."

The muscle tissue in the immediate proximity of the vaginal canal is in the area of greatest tension stress during labor. This sphincteric zone is most elastic

flabbiness, atrophy, or loss of function. With excessively long periods of passive immobilization, muscle reflexes become so impaired that actual paralysis is often simulated.

During the recent war, according to a war summary,¹² it was found that "loss of coordination is easier to prevent than to restore." "In the preservation or restoration of muscular function, nothing is more fundamental than the frequent repetition of correctly guided exercises" instituted by the patient's own efforts. "Exercise must be carried out against progressively increasing resistance, since muscles increase in strength in direct proportion to the demands placed upon them."

It would seem from the accumulated evidence that perineal exercises are especially important for two purposes: (1) to promote a return of normal muscle function in the immediate postpartum period and (2) to restore muscle function in women still in the childbearing age who, because of muscle-cell injury incurred at a more distant time, suffer relaxation of the pelvic musculature.

For the past fifteen years I have experimented with various means of exercising the perineal muscles. Any active exercise must be directed primarily toward drawing in the perineum. Only the exceptional woman, however, will continue the exercise long enough to produce results on mere instruction to do this. Many women, in addition, have no "awareness of function" and, unless provided with some way of knowing whether or not they are being successful, soon become discouraged or are unwilling to make even an initial attempt at exercise.

It seemed advisable, consequently, to devise some method by which the patient might see the results of her activity and be encouraged to continue her efforts—to give her an actual incentive to increase the contractile power of her perineal muscles and vaginal sphincters.

The principle of restoring the function of a segregated group of muscles with a specific aid, method, or program of re-education is well established through constant use in the fields of orthopedics, neuromuscular and plastic surgery, physical medicine and rehabilitation. Important specifications common to accepted methods of restoring function of injured skeletal muscles are means of segregation, guidance, and progression.

An early method studied was Fränkel's¹³ (1895) re-education program for locomotor ataxia. Methods recently developed for rehabilitation of the war injured and for establishment of awareness of function in patients with infantile paralysis gave valuable help in this study. The most recent developments in this highly important field are by Huddelston and Golseth¹⁴ and by Billig,¹⁵ who have devised a method of registering muscle action potentials on a loudspeaker, so that the patient hears increased sound when he is pulling more accurately with the muscle being trained for improved function.

The special sense which ordinarily activates the genital muscles is the tactile sense, which obviously cannot be utilized in training, on account of its hypersensitivity and exhaustibility. Sight is the most highly developed special sense for the guidance of skeletal muscle action, and in the restoration of perineal muscle function the response to sight sense guidance is instantaneous, with immediate understanding of the *modus operandi* by the patient.

The Perineometer

A pneumatic apparatus (Fig. 1) has been devised specifically for the exercise of birth canal muscles, with measurement of each muscular contraction visible to the patient. A chart (Fig. 2) is provided to keep a record of the accomplishment of each exercise period and serve as a progress guide for both patient and physician. The apparatus consists of a simple, balanced-resistance

numerous to permit some contraction, and when these muscles are actively exercised, the injured muscle cells are put to work at the same time. The incentive for reinnervation, regeneration, and re-education is the need for function of the muscle as a whole.

In the course of embryologic development, contractile muscle tissue is formed earlier than the nerves which supply it, and consequently muscle cells become secondarily innervated.⁶ This ability of a nerve fiber to establish a connection with a muscle cell is carried over into adult life, and a muscle cell which has lost its innervation may become reinnervated under favorable circumstances. Van Harreveld,⁷ Billig and van Harreveld,⁸ Arey⁹ and others have shown that striated muscle fibers atrophy when they lose their nerve supply but are capable of restoration when reinnervated. A single nerve fiber is capable of growing and of multiplying its branches many times, so that it may eventually supply a greater number of muscle cells than it did originally. To no group of muscles in the human body are the general principles of muscle-cell regeneration more applicable than to those injured in childbirth.

The need for some method by which perineal muscles may be preserved and developed has long been recognized. Hippocrates tried oil injections, hot douches and salves, and Soranus (A.D. 110) attempted support with the hand. Medical literature of the past century reveals that many obstetricians and gynecologists have felt that exercise or some other conservative means of reconstruction is indicated and should be of value during the childbearing age, but records of their efforts have been more or less relegated to the footnotes of gynecologic history. Exercises such as the assumption of the knee-chest position, walking on all fours, leg raising and early postpartum activity are valuable in aiding the uterus to resume its normal position and in improving the tone of the abdominal muscles. They do little, however, to affect the state of the perineum, and for its muscles special exercises are necessary.

Specific Exercise

In the current literature there is little mention of exercises to promote the restoration of perineal function, and it would seem that no satisfactory exercise has been found. One of the few references to exercise is that of Scott and Van Wyck,¹⁰ who described a procedure in which the patient contracts the gluteal muscles, at the same time drawing in the rectum as though to check the passage of feces through the lower bowel. Personal communications from many physicians indicate that it is a fairly common practice to instruct the patient to draw in the perineal region repeatedly.

One report of interest is that of Van Skolkvik,¹¹ who observed unusually firm perineae among a tribe of natives in South Africa. He found that it was the duty of the midwife, who was usually the mother or mother-in-law, to see that the young mother recovered perineal strength after childbirth. Exercise by contraction of vaginal muscles on distended fingers was begun several days after birth and was continued periodically for several weeks, until the desired result was obtained.

Past observations of obstetricians and gynecologists in relation to regeneration of muscle function are in accord with the conclusions reached concerning such regeneration through investigations conducted during World War II. Prior to the war, the accepted treatment of injured muscles was prolonged rest and passive exercise. It has been found, however, that heat, whirling water, expert massage, electrical stimulation and haphazard general activity have their place, though they have rarely made an injured muscle strong or prevented

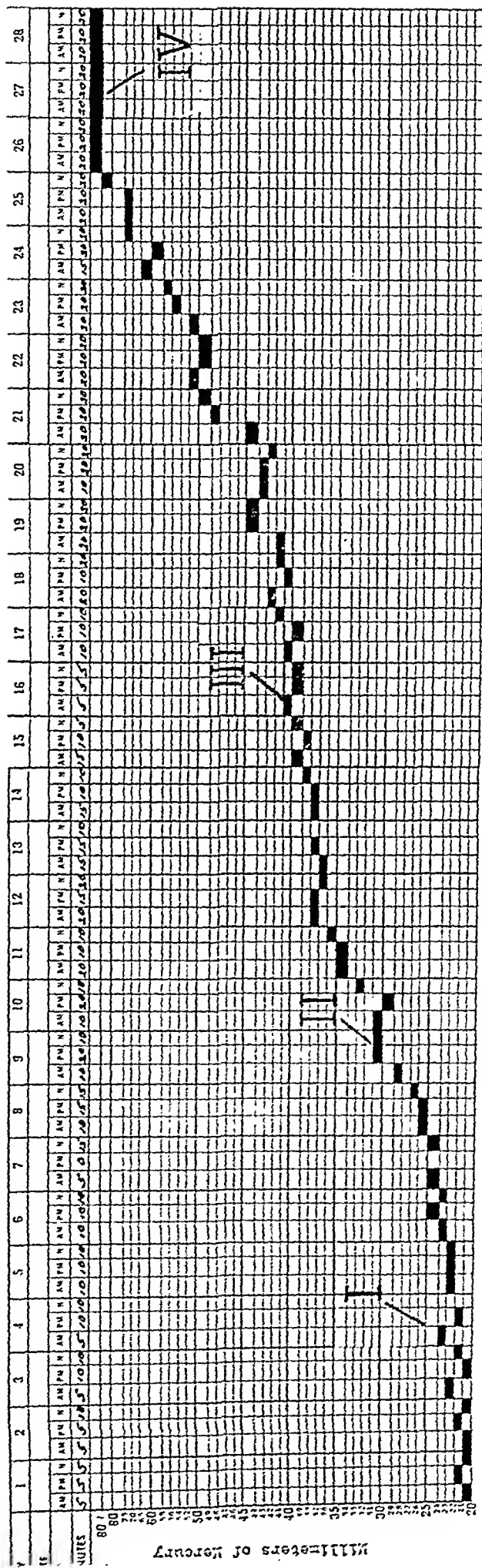


Fig. 2.—Exercise Chart of patient with lax anterior and posterior vaginal walls, gaping introitus and stress incontinence. The patient was instructed to exercise twenty minutes three times daily and to record the highest perineometer reading during each exercise period. The record of the initial five days of effort shows occasional weak muscular contractions at 20 mm. of mercury resistance. After twenty-five days of progressive exercise, muscular contractions are regular and strong at 50 mm. of mercury resistance. Clinically there is corresponding tightening of the musculofascial planes through which the vagina and urethra pass. Types of muscular contractions characteristic of four phases of development were taken during exercise periods at points I, II, III and IV and are shown schematically in Figs. 3, 4, 5, and 6.

pneumatic vaginal chamber operating at atmospheric pressure and connected by means of rubber tubing with a manometer calibrated from 0 to 100 mm. of mercury. In construction, the vaginal chamber is an anode-processed rubber cot of specified consistency, lightly stretched over a rigid slender core with a flange at each end. An air vent in the core connects the pneumatic chamber with the tubing and manometer. The base of the chamber is fitted with a round, semirigid rubber shield 8 cm. in diameter, which limits placement in the vagina

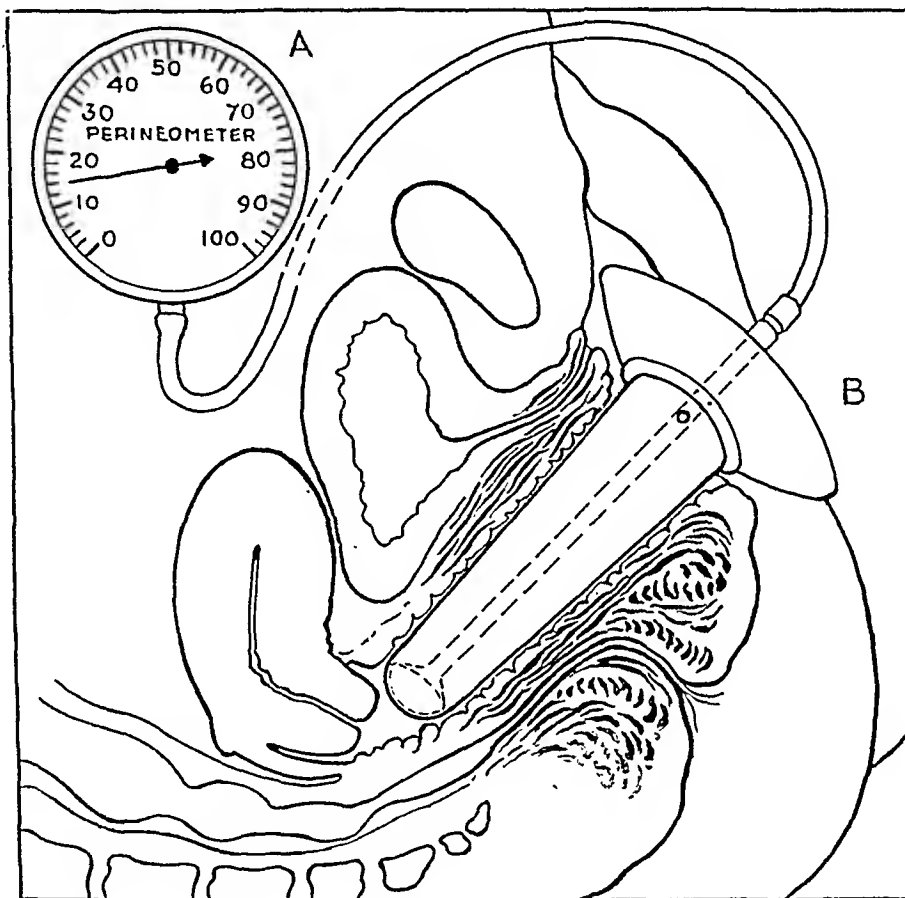


Fig. 1.—Diagram showing the Perineometer during Progressive Resistance Exercises of Lax Perineal Musculature. A. The manometer measures the force of perineal muscle contractions from 0 to 100 mm. of mercury during increasing resistance exercises. Visual guidance helps to establish awareness of function and coordination, and renders further exercise possible. The tubing is long enough to permit the patient to hold the manometer for observation. B. The pneumatic vaginal chamber receives the muscular contractions for conversion to sight sense perception. Conformity of the chamber to anatomic structure (length, 8 cm., diameter, 2 cm.) permits reconstructive exercise radially of anterior and posterior vaginal musculature and visceral extensions of the levator ani muscle.

and permits pivoting into position. The length (8 cm.) and diameter (2 cm.) of the vaginal chamber are in conformity with anatomic structures, especially with regard to the anterior and posterior musculature of the vaginal wall. In operation, any pressure from 0 to 100 mm. of mercury exerted on the pneumatic vaginal chamber is immediately registered by the dial of the manometer. The patient is instructed to insert the pneumatic chamber into the vaginal cavity so that the rubber disk rests against the perineum. She is then told to attempt to contract the muscles of the vagina while watching the dial on the gage.

Patients vary greatly in their ability to contract the vaginal muscles. Many, especially those with marked relaxation of the pelvic floor, are unable to register even a few millimeters of pressure on their initial attempts. Gradually, after

awareness of function and coordination, may be absent or brief or require as long as eight days. The second phase is a transitional phase. The third phase, or period of regeneration, is recognized grossly by the gradual increase of resistance registered. It is during this phase that a change in symptoms, such as relief of urinary incontinence, occurs. The phase of restoration is recognized by a leveling out of the resistance which the muscular contractions are able to overcome, usually above 60 mm. of mercury pressure. A leveling out at less than 40 mm. is an indication that the lower vaginal muscles have been active and that with continuation of exercise the muscles in a higher plane will show evidence of regeneration. To meet the latter contingency, one specification of the pneumatic vaginal chamber is that it shall be compressible but not expansible. If compression of one segment were to cause ballooning of another segment of the chamber, it would be possible for strong muscles to undergo development at the expense of weaker muscles.

While progressive resistance exercise with the aid of the Perineometer is useful whenever it is desirable to strengthen perineal muscles, work now being done in relieving urinary stress incontinence furnishes an excellent example of the efficacy of the method. To date (May 20, 1948), the condition has been relieved in 64 cases. Insufficient time has elapsed to justify a statistical report on this series, but the patient longest under observation has remained dry for fourteen months.¹⁷ Some of the women treated had worn pads continuously for as long as eleven years; others had undergone one to three plastic operations, without relief. There have been no failures when the condition was due primarily to relaxation or atrophy of the anterior vaginal muscles and the patient had at least partial control at times.

The method has been used also to improve tone of muscles and texture of tissues in the presence of anal incontinence, and apparently facilitated repair. A patient with rudimentary vagina and congenital absence of the uterus was instructed to use the "Perineometer" after plastic procedures to enlarge the vagina, and increased sphincter action from 0 to 40 mm. contractile strength.

Summary

The passage of the fetal head through the vagina during delivery is invariably attended by muscle injury. Excessive tension sever motor endplates attached to muscle cells from the terminal nerve filaments to which they

Fig. 3.—Muscular Contractions (I) taken from Phase of Initial Efforts to Contract Lax Perineal Muscles. Oscillations are slight and irregularly spaced. Although an attempt was made to contract muscles at regular intervals, only an occasional oscillation occurred. This is interpreted as being the result of absence of awareness of function or lack of coordination resulting from the detachment of muscle cells from nerve fibrils. This phase of efforts to gain coordination varies greatly, approximately 60 per cent of patients requiring only one or two exercise periods, while 40 per cent require up to eight days, depending on previous function.

Fig. 4.—Muscular Contractions (II) taken from Phase of Awareness of Function and Coordination. Oscillations have become more regularly spaced, indicating a recovery of awareness of function and a prompt response to effort. Variation in the height of the oscillations indicates that ability to control the degree of effort has not yet developed.

Fig. 5.—Muscular Contractions (III) taken from Phase of Regeneration. Oscillations are regularly spaced and are of almost equal height. This is interpreted as an indication of prompt response and an adequate control of effort. Increasing numbers of muscle cells are being reinnervated and are undergoing regeneration. The fact that muscular contractions are overcoming resistance at a single level, in this instance 40 mm. of mercury, indicates that the full strength of the muscles is being exerted and registered. Subsequent increases of resistance as shown in Fig. 6 are interpreted as the result of continued muscle regeneration and hypertrophy.

Fig. 6.—Muscular Contractions (IV) taken from Phase of Restoration. Oscillations regularly reach 80 mm. of mercury and the crest of each is rounded and prolonged. Marked increase in strength and in control of effort is revealed. Contraction is accompanied by less fatigue, and reserve strength exists. Palpable muscles are found to be firmer, thicker, and broader than before the institution of exercise. Evidence of improved function exists.

Note: Further effects of progressive resistance exercise on sphincteric and supportive muscle groups may be studied by tracing the course of linear force from anatomic point of action to fixed point of origin.

practice, and as the muscles become stronger through exercise, the pressure which can be exerted increases and frequently reaches 60 to 80 or more millimeters of mercury.

Since the instrument measures the degree of contraction of the perineal muscles, it has been called the "Perineometer." It is a simple pneumatic apparatus which functions only to show that muscular contraction is taking place and to measure the contraction. Its only action is to provide a medium between muscle action and sight. There is no provision to stimulate muscle contraction, nor does it provide for passive exercise in any way. The apparatus was constructed with the view that any pulsating or massaging action would defeat its purpose and would prove detrimental, harmful, and useless, and that, in the preservation or restoration of perineal muscular function, nothing is more fundamental than exercise instituted by the patient's own efforts.

Clinical Application

The initial test with the apparatus requires less than five minutes and is made in the course of physical examination. The patient is instructed to exercise twenty minutes three times daily and to record both the periods and the omissions of exercise on her chart. The period over which it is necessary to carry out this procedure varies principally in relation to the state of the perineum at the time exercises are commenced and to the diligence of the patient. Initial presence or absence of awareness of function and coordination also is an important factor. An occasional patient may experience great difficulty in gaining awareness of function.

Restoration of tone and function to lax or atrophied perineal muscles requires from twenty to forty hours of progressive resistance exercise, spread over twenty to sixty days. As a rule, young patients progress more rapidly than older ones, but one woman of 58 increased her contractile strength from 10 to 100 mm. of mercury without undue effort in thirty days. The period required for maximum results varies also according to the purpose for which Perineometer exercise is prescribed, whether to restore tone and function in the immediate postpartum period, to improve early cystocele or rectocele during the child-bearing years, to improve the vaginal muscles so that a contraceptive diaphragm may be retained,¹⁰ or to relieve urinary stress incontinence. When satisfactory results are not achieved in a reasonable period, the patient may be exercising abdominal, gluteal, or other extraneous muscles to affect dial readings. Backache or abdominal distress also suggest that the wrong muscles are being used. The patient who complains of fatigue probably is exerting greater effort than is necessary. For these reasons the patient should be seen at least once a week, so that her efforts may be properly directed.

While the patient is exercising regularly, she is encouraged to attempt to increase the pressure 1 to 2 mm. of mercury daily and to keep a record of the maximum contraction of which she is capable at each exercise period. For this purpose the graphic chart has been prepared, to enable her to record the pressures registered on the dial. The actual record kept by one patient is shown in Fig. 2. With minor variations any woman with reasonable diligence may duplicate the record shown.

The types of contractions of which this patient was capable as she continued with her exercises and evidenced progressive restoration of function are shown in Figs. 3, 4, 5, and 6. While the period necessary for maximum restoration of function by exercise may vary, it is possible to discern three or four phases of development. The record chosen for illustration shows four phases rather evenly distributed over four weeks. The first phase, the period required to establish

are normally connected. This partial loss of innervation is in large measure responsible for the relaxation of perineal muscles so commonly observed after childbirth.

Experience has shown that a demand for use is the most important factor in restoring the functional capacity of any skeletal muscle. Active exercise will aid in the reinnervation of injured muscle cells and will bring about a return of normal contractility.

The shorter the time elapsing between muscle injury due to childbirth or a surgical procedure and the beginning of exercise, the less will be the amount of tissue atrophy and the shorter will be the time necessary to re-establish normal function.

Exercise with the Perineometer is useful in restoring function and tone in the immediate postpartum period, improving early cystocele and rectocele during the childbearing years, improving the vaginal muscles so that a contraceptive diaphragm may be retained, and relieving urinary stress incontinence.

Surgical procedures for the correction of vaginal, urethral, and rectal incompetence may be facilitated by preoperative and postoperative exercise which improves the texture, tone, and function of perineal muscles.

The "Perineometer," an instrument devised to register muscle contraction, is of great value as a visual aid in guiding the patient during the course of her exercises and in encouraging her to continue until the desired result is attained.

The method of exercise described suggests a new approach to the studies of perineal physiology as related to physics.

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Fig. 3.



Fig. 4.

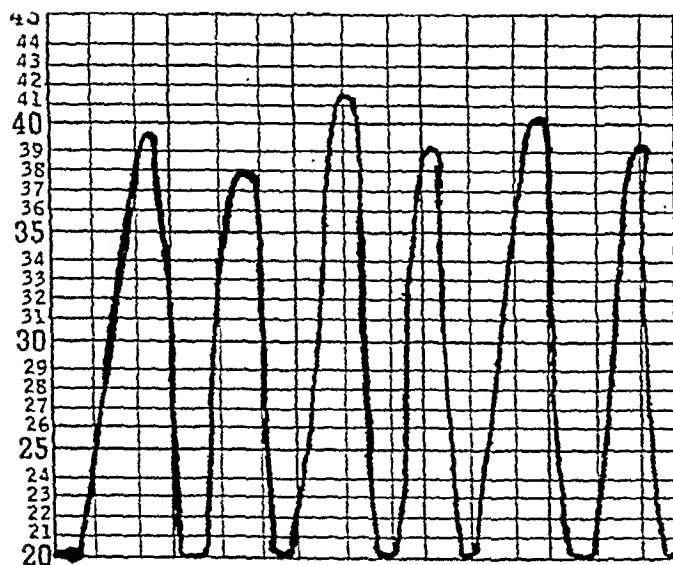
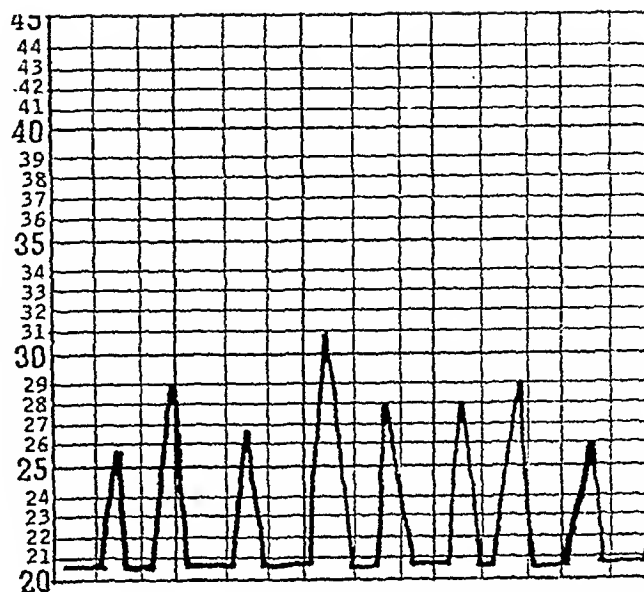


Fig. 5.

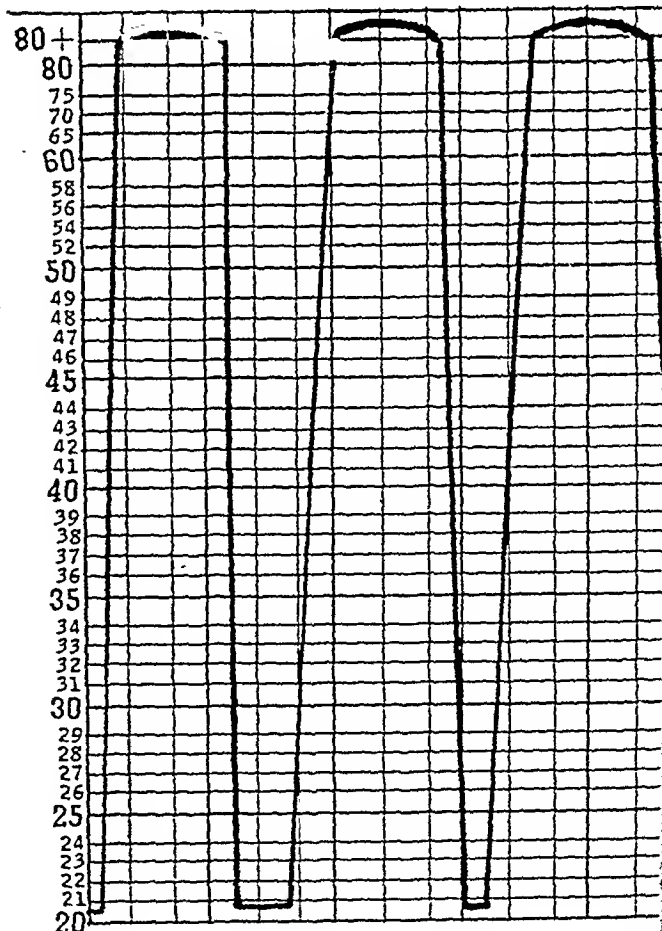


Fig. 6.

(See legends on opposite page.)

2. *Adhesive Vaginitis*.—Retraction, fibrosis, and adhesions of the vaginal mucosa. This process may be so extensive that the vagina becomes partly or completely obliterated.

3. *Factitial Cystitis*.—Varying degrees of cystitis are encountered, ranging from simple episodes of oliguria and hematuria to far advanced instances where gross prolonged hematuria, intractable pain, and chronic infection are present. Cystoscopic examination in these cases reveals varying degrees of necrosis and slough of the bladder mucosa.

4. *Ureteral and Urethral Obstruction and Stenosis*.—These may give rise to such insidious symptoms as anuria, incontinence, hematuria, pain, and occasional manifestations of hydronephrosis, uremia, and death.

5. *Destruction by Fibrosis of Regional Lymphatic Nodes and Vessels*.—Evidence of elephantiasis in one or both extremities may follow.

6. *Sterility and Onset of Menopausal Syndrome*.

7. *"Frozen" Pelvis*.—Irradiation may cause adhesions of omentum and intestines to pelvic organs, giving rise to symptoms of pain, intestinal obstruction, and the so-called "frozen" pelvis. Encroachment may extend to nerve trunks, giving rise to constant pain in the pelvis and thighs.

8. *Transient and Permanent Rectal Pathology*.—

- a. Radiation sickness. This entity is included in this general group as it must be considered a precursor to the lesions which develop subsequently.
- b. Factitial proctitis.
- c. Rectal fibrosis without stricture.
- d. Rectal stenosis or stricture.
- e. Rectovaginal fistula.
- f. Secondary or metastatic carcinoma.

The paper will attempt to present certain interesting aspects of the latter group.

Material

A series of six hundred cases encountered in this hospital over a thirteen-year period commencing Jan. 1, 1934, and continuing to Jan. 1, 1947, was reviewed. The cases comprised the following:

1. Squamous cell and adenocarcinomas of the cervix.
2. Adenocarcinomas and sarcomas of the corpus uteri.
3. Ovarian carcinoma.
4. Primary carcinoma of the Bartholin gland.

Dosage varied markedly in individual cases. In most instances, dosage was determined jointly by the departments of gynecology and radiology. Factors determining dosage included:

1. Type and location of lesion.
2. Individual tolerance as determined by reaction to previous therapy.
3. Type and amount of therapy obtained elsewhere.
4. Time elapsed between therapy.

Treatment in the six hundred cases consisted of:

1. X-rays only.
2. Radium or radon, either in applicators or in permanently inserted gold seeds.
3. Combinations of x-rays and radium emanations.
4. Combinations of surgery and/or x-rays and radium emanations.

INTESTINAL CHANGES SECONDARY TO IRRADIATION OF PELVIC MALIGNANCIES

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IN THE treatment of malignancies of the pelvic organs in the female, there are few complications more vexing and occasionally difficult to evaluate properly than the numerous pathologic entities which arise subsequent to radiation therapy. While a veritable legion of distressing complications may develop to harass both the gynecologist and radiologist who have collaborated in treating a pelvic malignancy, none probably has the potentialities of plaguing the patient as early, as violently, or as prolongedly as do such disorders of the rectum and sigmoid as can be visualized proctoscopically and which develop all too frequently.

When a diagnosis of malignancy is made, the mode of therapy to be employed should be chosen only after the type of lesion and the patient's age and systemic condition have been thoroughly investigated and evaluated. Where such study is engaged in, subsequent complications can be predicted with a fair degree of accuracy; for example, where a fundal or ovarian malignancy is treated by surgery and the surgical intervention is preceded by or followed by a single course of deep x-rays, the permanent damage to the tissues will probably be minimal in incidence and severity. However, if a case of cervical carcinoma or a fundal malignancy which is inoperable or for which surgery would be poorly tolerated is treated by a systematic regime of deep therapy, consisting of an initial series of deep x-rays followed by insertion of radium and then another course of deep x-rays, the incidence of permanent damage, especially to the terminal portion of the bowel, rises markedly, presenting in its wake disturbing and provoking problems. Far too frequently the triumphant arrest or even complete cure of a malignancy is obscured by the disastrous damage inflicted to surrounding tissue by x-rays and radium therapy.

It is a recognized and accepted fact that unless deep therapy is administered in sufficient dosage to bring about certain irreversible changes in the irradiated area, the malignancy to be treated will not be eradicated or arrested. Indeed, it is safe to assume that small dosages of x-rays or radium emanations are without benefit or, worse still, may act in a stimulating capacity upon the tumor to be destroyed. With that concept established, we must acknowledge that one or more of the following entities must ensue if therapy is to be considered adequate.

1. *Initial Erythema of the Skin, Followed by Tanning and Fibrosis.*—Advanced stages may reveal slight to severe telangiectasia. X-ray burns accompanied by deep slough and necrosis occasionally are the ultimate results.

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treatment. Frequently, symptoms are so severe that death ensues. In this series, no deaths from radiation sickness were encountered. It can readily be seen that the gynecologist might well waver in his conviction to pursue a full course of treatment in a patient who has become violently or critically ill during an initial series of x-ray administration.

That radiation sickness may be considered a harbinger of things to come can be gleaned from the findings that all cases of permanent rectal damage in the series were preceded by radiation sickness.

Symptoms of radiation sickness are usually precise and offer no particular diagnostic problem. The patient's first complaint is nausea and lack of appetite. Emesis may or may not be experienced. Lassitude is common. Headache and nervous manifestations are frequent, especially so in the emotionally unstable patient. Psychic disturbances in this group are probably precipitated by morbid tendencies rather than mechanical factors. Nausea and emesis are followed by tenesmus and diarrhea. Stools become increasingly frequent and, although formed elements may be present in the early phases, they become progressively more watery. Mucus is conspicuously absent until the condition has become severe. The anus becomes inflamed and painfully tender from gastric acid not neutralized in its passage through the intestines due to hyperperistalsis. In severe or uncontrolled cases, complete upset in physiological balance, starvation, and dehydration may result.

Proctoscopic examination during the active phases of radiation sickness obviously would be extremely painful. For this reason solely, no proctoscopic study should be undertaken at this period of the illness. Examination undertaken in a few isolated cases, however, revealed the bowel to be distended and markedly hyperplastic. Grossly, the bowel appears to be puffy and this is due to the extensive edema which is present in all layers. The mucosal layer, usually microscopic in thickness, can be measured in millimeters. Before death, stripping of the mucosa is curiously enough absent, despite the edema and hyperperistalsis prevailing at the time. Only when the patient is in extremis or following death does stripping of the mucosa occur with ease.

That the entity is not at all clearly understood is apparent from the numerous varieties and types of therapy which have been suggested in the literature and which are directed toward preventing onset of the illness as well as alleviating the condition when it occurs. Cyclic vogues of treatment have been employed and subsequently rejected on our service as they no doubt have been elsewhere. A review of the thirteen-year period reveals that such medications as cod liver oil, crude liver extract, orange juice, multiple vitamins, B-complex vitamins, fractions of the B-complex stressing thiamine chloride and pyridoxine, sedatives, hydrochloric acid, opium by mouth, and opium and belladonna suppositories have all been employed and found wanting in efficacy.

At present, when radiation therapy is administered to a patient on our service, careful vigilance is maintained to ascertain immediately when the entity manifests itself. Therapy, for the most part, is empirical but, wherever practical, the specific problem is treated individually. A bland diet is instituted at once. Despite lack of appetite, frequent small feedings and high fluid intake are urged. Vitamins and their fractions are usually prescribed where indicated. With the onset of diarrhea, in addition to the above outlined regime, tincture of camphorated opium and milk of bismuth are administered. Sedation in the form of barbiturate suppositories is administered about one hour prior to the x-ray exposure. Additional sedation during the day and at bedtime is freely employed and should be ample. In uncontrolled cases, where upset in electrolyte balance occurs, with resulting dehydration together with starvation, five to ten per cent glucose solutions fortified with vitamins and amino acids must be given

Pertinent aspects of each group of lesions are individually discussed under appropriate headings.

Cases treated only by surgery or which, upon examination at first admission, were considered hopeless were omitted from the series. In Table I, the lesions present are classified, including the number and percentage of the total series, and the percentage as computed for the seventy cases involved by irreversible

TABLE I

| | FACTITIAL PROCTITIS | FIBROSIS WITHOUT STENOSIS | STENOSIS | RECTO- VAGINAL FISTULA | FISSURE | OBSTRUC- TION | SECONDARY CARCINOMA |
|--|------------------------|---------------------------------|----------|------------------------------|---------|------------------|--|
| Total | 59 | 1 | 48 | 13 | 2 | 11 | 10 and 1 primary adeno- carcinoma |
| Per cent in series | 9.93 | 0.16 | 8.0 | 2.16 | 0.33 | 1.83 | 1.83 |
| Per cent in 70 cases of permanent pathology | 84.28 | 1.42 | 68.57 | 18.57 | 2.85 | 15.71 | 15.71 |

lesions. Table II presents classification of symptoms primarily experienced, together with the average time interval between administration of initial deep therapy and onset of symptoms. Onset of various symptoms is expressed in weeks. Note extremely high incidence of bleeding.

TABLE II

| | BLEEDING | CONSTI- PATION | DIARRHEA | PAIN | OBSTRU'C- TION | FECES THROUGH VAGINA |
|---|----------|-------------------|----------|-------|-------------------|----------------------------|
| Average time of onset of symptoms in weeks | 72.06 | 85.26 | 39.05 | 76.31 | 110.68 | 106.15 |

I. Immediate or Transient Complications

A. *Radiation Sickness*.—Of the six hundred cases reviewed, 523 patients, or 87.16 per cent, experienced radiation sickness at some time during the period of treatment or immediately thereafter. In some instances symptoms did not appear until the patient returned to her home.

Radiation sickness is a bizarre entity and its pattern of onset and course unpredictable. The physiologic mechanism producing the condition has been extensively speculated upon, but definite proof is lacking to explain its many phases or why therapy directed toward correcting it is so unsatisfactory. Changes in electrolytic balance, alteration of internal secretions, creation of adverse electrical potentials are suggested. The cardinal point of interest is that, secondary to some unknown mechanism, a definite demonstrable change does occur in the mucosa of the gastrointestinal tract. Onset of symptoms may follow a single exposure to x-rays. The patient may become ill at any point in the initial series, or, as pointed out previously, immediately after completion of the series. A given patient may be subjected to an entire course of irradiation therapy without ill effects of any kind. The usual picture, however, follows a pattern similar to this: A course of x-rays, radium, and x-rays to be administered at six- or eight-week intervals, barring reaction complications, has been decided upon. Radiation sickness is present with the initial series of x-rays and again when the radium is inserted but fails to appear with the second series of deep x-rays. In another patient, the appearance of symptoms may be reversed. In brief, the condition may be present or absent with any or every phase of

Specific symptoms develop in the order of diarrhea, bleeding, pain, constipation, and finally fistula and obstruction. The mean average for the fifty-nine cases, including all symptoms, is 81.58 weeks between initial treatment and onset of first symptoms. Wherever higher dosages of x-rays or radium emanations were employed, symptoms occurred considerably earlier.

The symptoms complained of are numerous. The cardinal symptom, and incidentally the source of greatest concern to the patient, is bleeding from the rectum. The stool may be only slightly streaked by bright red blood or bleeding may be profuse and accompanied by clots and mucus. Frank hemorrhage is common in severe cases. Although diarrhea is present in some cases, constipation is more frequently the rule and may be extremely troublesome in late cases. Defecation is painful and difficult. Straining at stool is almost universally necessary. A bearing down sensation is frequently present. In some cases, large strips of mucus are passed at stool. Stools may be ribbon-like if narrowing of the bowel lumen indicating early stricture is concurrent. Anemia induced by blood loss gives rise to such secondary symptoms as dyspnea, weakness, and lowered systemic resistance. Weight loss may be noted. The appetite is poor. Morale is often low and this, coupled with a neurotic state, may breed morbid tendencies. In the advanced cases, the patient becomes chronically and often seriously ill. Careful study of her condition is imperative if a favorable prognosis is hoped for. It frequently becomes necessary to employ drastic measures at this point, rather than to assume an air of hopeless resignation and relegating the patient to her fate as an incurable invalid.

With symptoms in evidence, such as those just described, in a woman who has been treated extensively by radiation therapy, the diagnosis of factitial proctitis is readily made. When a patient is seen in the tumor clinic or is readmitted to the hospital on our service with one or more of the complaints listed, consultation with the proctologist is immediately arranged in an endeavor to confirm exactly what type of lesion exists. In small communities which cannot boast of a trained gastroenterologist, establishment of an accurate diagnosis is frequently difficult or impossible. Where such a situation prevails, every effort should be expended to assure proper evaluation of the case. This is extremely desirable in that rectal malignancies must be screened out.

In early or primary factitial proctitis, the bowel, on proctoscopic examination, shows a diffuse erythematous change in the mucosa. The membrane appears thickened as well as reddened and is edematous with increased friability evident. The portion of the bowel which has undergone most change is the area just opposite the cervix. This area is roughly four to five inches from the anus and approximately at the rectosigmoid junction. The changes described are more marked where radium emanations have been employed. This is easy to comprehend when the close proximity of the cervix to the rectum is borne in mind. Reaction is universally more severe, the incidence higher, and onset period earlier where radium emanations are employed.

As the process becomes more severe and enters the secondary stage, the lumen of the bowel narrows progressively. The mucosa now becomes thinned and there is evidence of a patchy fibrosis. Scattered throughout the areas undergoing scarification countless telangiectatic changes are noted. With continued fibrosis, the lumen of the bowel narrows even more. The mucosa becomes increasingly pale and a weeping exudate becomes evident. Again these changes are limited to the area of the rectosigmoid junction. The changes are irreversible. They are instituted in the early stages when a spasm of the small vessels causes a relative ischemia of the surrounding tissue. Further spasm due to the ischemia precipitates infarction, thrombosis, and eventual scarring.

Management of factitial proctitis is difficult and discouraging at best. Efforts should be directed toward making the patient comfortable rather than

intravenously. If serum proteins are alarmingly low, plasma should be administered. Frequently, in the most severe cases, it becomes imperative to transfuse the patient liberally with whole blood if the above measures fail to elicit a fair degree of response.

Unless daily visits by the physician are possible, a patient suffering with radiation sickness should not be discharged from the hospital. When symptoms are subsiding and all indications point to recovery without recurrence, discharge may be granted but instructions as to diet and activity should be clearly explained. Fortunately, recovery from radiation sickness is rapid as soon as therapy is stopped but in some instances complete recovery is occasionally prolonged for a considerable period of time. This factor was very prevalent in the very aged and debilitated cases treated.

II. Delayed and Permanent Complications

The delayed and permanent complications observed in the series studied numbered seventy, or 11.66 per cent. This is a considerably smaller number of cases than were encountered with radiation sickness. It must be understood, however, that this number represents only the cases where diagnosis of the permanent rectal lesion was confirmed by digital examination, the proctoscope, and barium enemas. Unfortunately, the two latter procedures were not routinely employed when patients returned to the tumor clinic or when they were again hospitalized. Fifty-nine cases of the series were diagnosed as factitial proctitis. Simultaneously present in most of these cases or developed as sequelae were forty-eight instances of stenosis of graded severity. Ten cases in the series suffered with metastatic extension of the pelvic malignancy. Thirteen developed rectovaginal fistulas and one an ulcerative fissure in ano. One case was complicated by a primary adenocarcinoma of the rectum.

We must assume that these conditions are present in a considerably higher percentage of the cases treated but because the manifestations are so benign the patient is not seriously incapacitated or even annoyed. It would perhaps be entirely safe to estimate that 50 to 75 per cent of all women treated, knowingly or otherwise, bear permanent rectal residual changes. This estimate is based on the incidence of radiation sickness encountered.

A. Factitial Proctitis.—In the complications to be anticipated following radiation therapy, perhaps no single entity proves a source of greater concern and vexation to the gynecologist than does factitial proctitis. By definition, proctitis is an inflammation of the rectum. Medical dictionaries define the term "factitial" as something produced "unintentionally" or by "artificial means"; hence the proctologist's terminology to describe a rectal lesion produced unintentionally. The lesion varies in severity from minimal mucosal changes to extensive ulceration as will presently be described.

As previously stated, fifty-nine cases in the series were diagnosed as factitial proctitis. This represents 9.83 per cent of the total series, or 84.28 per cent of the permanent lesions. Five of the fifty-nine cases of factitial proctitis were treated with x-rays only, three with surgery and x-rays, and the remaining fifty-one with combinations of surgery, x-rays, and radium emanations. Dosage varied markedly; the lowest dosage of radium emanations delivered was 840 mc. hr., the highest 6173 mc. hr. The lowest number of roentgen units delivered by x-rays was 600, the highest 8,000. Onset of symptoms following therapy cannot be predicted. The period of time elapsing between initial therapy and final treatment and appearance of symptoms and subsequent diagnosis varies greatly. The longest period of elapsed time between initial treatment and reported onset of symptoms was 278 weeks, the shortest period 28 days.

Table III classifies and evaluates the therapy employed in all seventy cases.

TABLE III

| | NO IMPROVEMENT | | PARTIAL IMPROVEMENT | | MARKED IMPROVEMENT | | NO TREATMENT HOPELESS | |
|--|----------------|----------|---------------------|----------|--------------------|----------|-----------------------|----------|
| | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT | NO. | PER CENT |
| Combination of palliative therapy outlined | 10 | 14.2 | 4 | 5.1 | 6 | 8.5 | 6 | 8.57 |
| No therapy | 7 | 10 | 3 | 4.2 | 9 | 12.8 | | |
| Recent regulated regime | 2 | 2.8 | 2 | 2.8 | 11 | 15.7 | | |
| Colostomy | 6* | 8.57 | 1 | 1.4 | 3 | 4.2 | 6* | |

*Listed under both "No improvement" and "No treatment—hopeless" headings.

B. *Rectal Stenosis or Stricture.*—Rectal stenosis following irradiation to pelvic organs results from the scarring and shrinking of the bowel secondary to the faetitial proctitis. That the process is instituted even before the proctitis completely subsides is evident from proctoscopic examination. Degree of fibrosis is dependent on degree and severity of the proctitis. In this series, forty-eight patients, or 8 per cent, developed stenosis as established by proctoscopic examination or barium enema. Of these, only four were not preceded by a diagnosed case of faetitial proctitis and all four cases revealed only minimal stricture. Again, we must assume these four patients probably experienced a faetitial proctitis which was so benign in its course that no symptoms were noticed. The value of routine proctoscopic examinations in all patients treated by irradiation is again evident here.

On proctoscopic examination where fibrosis and stricture exist, considerable difficulty is experienced in passing the scope. The lumen is greatly reduced in caliber. The mucosa is pale, fibrotic, and complete stenosis may be in evidence in the final stages. Where scarring is not too excessive, the telangiectasia may still be visualized but in cases showing very extensive fibrosis, these findings may be completely obscured by scar tissue.

Symptoms, which obviously appear later than in cases suffering with faetitial proctitis, are similar in some respects to those experienced in that entity. Constipation is the cardinal symptom. Passage of stools is painful and difficult and may be impossible if the stool is hard. Occasional streaking by bright red blood is noted on the stool. This results from an actual tear in the mucosa due to fibrosis and lack of elasticity. In numerous instances, resulting fecal impactions convey a sense of bearing down in the pelvis. Intestinal obstruction may readily occur.

Treatment is conservative unless acute or chronic obstruction occurs, in which case a simple loop colostomy should be performed. In treating the condition conservatively, a bland diet is of paramount importance. Mineral oil, muciloid preparations, and saline or soapsuds enemas may be employed if the tendency to constipation becomes too marked.

C. *Fibrosis Without Stricture.*—Only one case of rectal-mucosa fibrosis uncomplicated by stricture was observed in this series. The patient's chief complaint was occasional rectal bleeding but there were no other symptoms. On proctoscopic examination, the lumen of the bowel was normal in size but the mucosa densely fibrotic. About two inches above the anus there was a small ulcerative fissure. A biopsy was obtained and reported benign. Treatment consisted of cauterizing the base of the ulcer and placing the patient on a bland diet. Recovery was rapid and complete.

It is interesting to speculate at this point what percentage of the cases having received deep therapy eventually developed fibrosis without stricture of the rectal mucosa.

expending futile attempts at re-establishing the normal appearance and contour of the bowel. Healing with fibrosis but with a minimum of stricture is the ideal end result. Treatment is either radical or conservative, the former consisting of a simple loop colostomy with no attempt to dissect out the rectum. Indications for the procedure are:

1. Prolonged and profuse bleeding which has failed to respond to conservative therapy.
2. Acute or chronic bowel obstruction.
3. Starvation.
4. Dehydration.
5. Progressive symptoms other than rectal bleeding despite conservative therapy.

Colostomy was resorted to in ten of the cases. This represents 14.28 per cent of the seventy cases permanently involved, or 1.66 per cent of the entire series.

In five of these cases bleeding continued or subsequently reappeared due to metastatic invasion of the bowel. One patient continued to experience rectal bleeding by virtue of the factitious proctitis failing to heal. The remaining four cases obtained partial to complete relief from rectal symptoms. None of the patients had closure of their colostomies performed subsequently, even though symptoms subsided. In every instance this possibility had been explained to the patient.

Conservative treatment employed on the service over the thirteen-year period included the following:

1. Soothing and anesthetic rectal ointments.
2. Opium and belladonna suppositories.
3. Paregoric and bismuth where diarrhea prevailed.
4. Mineral oil and saline enemas where constipation prevailed.
5. Hydrochloric acid.
6. A bland diet.
7. Vitamin and iron preparations.
8. Blood and plasma in extreme cases.

These medications are representative of conservative treatment employed, and the degree of success achieved through their use was unsatisfactory and unpredictable. Some cases responded to therapy, others did not. A few seemingly cleared up spontaneously without therapy. Recently, in a group of fifteen patients, we employed the following regime with eleven cases showing marked to complete improvement, two showing partial improvement, one case failing to respond and one other subsequently developing a metastatic carcinoma of the rectum.

1. Muciloid preparations.
2. A bland, well-balanced diet.
3. Phenobarbital and extract of belladonna one-half hour before meals and at bedtime.
4. Iron preparations and ascorbic acid in large doses when anemia is marked.

The rationale for the regime outlined is simple. Muciloid preparations provide soft gentle bulk in the stool and simultaneously coat the irritated bowel. The combination of phenobarbital and belladonna relax spasm of the bowel and tend to eliminate hyperperistalsis. In addition this combination may have a beneficial effect on the psychotic factors that are present so frequently. The bland diet, iron and ascorbic acid need not be elaborated on. Although the series obviously is too small to draw a definite conclusion, the results obtained seem to warrant serious consideration.

were also squamous-cell carcinoma. In one case, where the primary lesion had been a squamous-cell carcinoma of the cervix, the malignant rectal lesion was found by biopsy to be adenocarcinoma. The coexistent primary rectal carcinoma caused a flurry of questioning and debate, but the final decision was that the patient actually was suffering from two distinct lesions rather than a primary and metastatic one. One fundal and one ovarian adenocarcinoma metastasized to the rectum. As previously stated, rectovaginal fistula was present in five of these cases.

Metastasis to the rectum from a primary uterine malignancy is readily comprehended when the close anatomical relation of these organs is remembered. Nine of the patients in this group had expired and the remaining two had been discharged to their family physicians as hopeless cases at the time this paper was prepared. In all instances, the primary malignancy had failed to respond to therapy and extensive pelvic metastasis had ensued. It is interesting to speculate whether the combined factors of lowered systemic resistance, anemia, and devitalization of the local tissues might not favor the growth of these metastatic lesions.

Symptoms of rectal carcinoma secondary to a primary pelvic malignancy in women are similar to those encountered in severe factitial proctitis. Individual manifestations are more severe, however, especially in the advanced stages. Bleeding is again the cardinal symptom. Stools may be only occasionally streaked by bright blood or continuous bleeding may be evidenced. Gross hemorrhage may occur. One of the cases reported in this group succumbed during such an episode. The normal stool habit becomes disrupted. Unlike the prevailing tendency to constipation as evinced in factitial proctitis, diarrhea and constipation may alternate. Loose, frequent stools with blood and mucous present may be the cardinal symptom. Pain is transitory and may or may not be present. Straining at stool, signs and symptoms of obstruction, and a bearing down sensation may be present. If a patient presents evidence of marked anemia, weight loss, and debilitation, rectal carcinoma should be strongly suspected. Where these latter three symptoms are present, metastases to other parts of the body frequently have occurred simultaneously.

Diagnosis of the entity is fairly easy. On digital examination, the lumen is narrowed as in most cases of factitial proctitis. However, instead of a more or less rigid bowel wall, a friable mass is encountered if the lesion is sufficiently low. In these cases the examining finger comes away blood streaked. On proctoscopic examination the lesion is readily visualized as a friable mass which bleeds easily and breaks away in fairly large pieces. Where invasion is early, the thickened wall of the bowel may show only a small amount of ulceration. Occasionally, the lesion does not invade the lumen but encroaches on the serosal surface of the gut. In these cases, accurate diagnosis becomes difficult or impossible. Indeed, several cases suspected of being involved by a metastatic malignancy to the rectum were proved otherwise at laparotomy. In others, symptoms subsequently subsided. Barium enemas must be resorted to in those cases where proctoscopic examination is difficult, too painful, or where the scope can be passed only for a very short distance. Filling defects are fairly easily identified by this method. Wherever possible, biopsy of the suspicious tissue should be obtained to confirm or refute the diagnosis.

On our service, treatment in these cases is entirely palliative and empirical. Opiates are prescribed for pain if this symptom is severe. Bland diet to prevent additional irritation to the distressed bowel is employed. Occasionally, transfusions are employed, purely as a humane gesture. One patient received a loop colostomy in this group. Surgery was performed to relieve an obstruction and excessive bleeding.

D. *Rectovaginal Fistula*.—Rectovaginal fistula occurred in thirteen patients in the total series. This represents 18.5 per cent of the cases with permanent rectal pathology, or 2.16 per cent of the total series. The earliest fistula to appear following onset of therapy was discovered in eleven weeks. The longest elapsed period from onset of therapy to appearance of the fistula was 582 weeks. In two cases, subsequent spontaneous closure occurred. In these two cases and in one other which did not heal, there was no extension of the pelvic malignancy but the vaginal tissues were extremely pale, fibrotic, and devitalized. Five cases in the group were further complicated by metastatic carcinoma of the bowel and five revealed extensive metastases to the vaginal floor. In each of these ten cases, the defect had obviously occurred due to the encroaching malignancy, since the tumor mass extended from vagina to bowel. One case was treated by colostomy because of extensive stenosis at the rectosigmoid junction, causing almost complete obstruction.

Rectovaginal fistulas in patients treated for pelvic malignancies by irradiation probably occur due to these changes:

1. Extensive irradiation decreases bowel elasticity.
2. The bowel becomes thin and fibrotic.
3. Rectovaginal septum becomes thin, fibrotic, friable.
4. Fibrosis and ischemia prevent healing of small traumatic fissures resulting from hard large stools. This increases the hazard of perforation by trauma.

Passage of hard rubber douche and enema tube tips adds to the traumatic element. It is doubtful whether sexual intercourse would cause a breakdown unless the vaginal wall is extensively necrotic such as is evidenced in certain far advanced metastases.

It has been pointed out that five of the cases in this group had metastatic carcinomas to the rectum. Five other metastatic carcinomas of the rectum were encountered in which the metastatic lesion occurred somewhat higher than the rectosigmoid junction. This would tend to confirm the opinion that only where the metastatic lesion involves or approximates the vaginal vault does rectovaginal fistula occur readily secondary to the carcinomatous invasion of the bowel.

Symptoms of rectovaginal fistula consist of passage to, and escape through, the vagina of gas and feces. In the cases where defects were secondary to carcinoma by metastases, occasional episodes of vaginal bleeding were reported. Examination by speculum was necessary to differentiate between bleeding caused by the primary pelvic lesion and the ulcerated edges of the fistula. Where the fistula is small, there may be no symptoms whatsoever, if the stool is firm and well formed. Diagnosis is confirmed by observing feces in the vagina or noting bubbling of gases through the defect. In the absence of these two signs, a probe may be passed through the defect if a lesion is suspected.

Radical treatment is never attempted in these cases. Surgical measures are doomed to failure in cases showing even minimal defects, since the tissue involved is so fibrotic and devitalized that healing would not occur. Where malignancy is absent, the employment of a bland diet and muciloid preparations in an effort to create a soft yet bulky stool is frequently beneficial. Douches and enemas should be administered with great care to prevent additional injury. Where malignancies exist, any treatment attempted would merely plague the patient and is therefore inadvisable.

E. *Secondary Carcinoma*.—A total of eleven patients, 15.7 per cent of the seventy cases with permanent rectal pathology, or 1.83 per cent of the total series, had rectal carcinomas. Lesions were diagnosed by proctoscopic examination and barium enema with confirmation by biopsy. Eight cases were secondary to squamous-cell carcinomas of the cervix and on biopsy the rectal malignancies

TISSUE LOCALIZATION AND EXCRETION ROUTES OF RADIOACTIVE DIBROMESTRONE*

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THAT the steroid hormones, which are secreted or absorbed into the blood stream and carried in it throughout the body, should have a selective action on the epithelium of the pituitary, breast, uterus, vagina, or prostate and seminal vesicles, and not upon the other cells of the body, admits of two possible explanations. Either these epithelial cells are easily stimulated by steroid hormones, are sensitive to them in infinitesimally small amounts, or the steroids may be selectively absorbed by the reacting organ so that the concentration becomes much higher there than elsewhere in the body. The fashion in which iodine becomes localized in the thyroid gland might suggest the latter mechanism. That no one has conclusively demonstrated which occurs in the body, selective sensitivity of the end organs, or selective absorption by them, is largely attributable to the inadequacy of methods of extraction and purification of hormones from tissue and of assay after such purification. For instance, in 1934, Geschickter, Lewis, and Hartman⁸ carried out studies of the estrogenic content of fibroadenomas of the human female breast and later (Lewis and Geschickter¹⁰) of fibromyomas of the uterus. These tumors were said to be high in estrogens, but the interest aroused by these observations was dissipated when Frank⁷ and his co-workers demonstrated equally high titers in normal female muscles. Other workers have been unable to find estrogenic activity in any of these tissues.

Were it possible to synthesize steroid hormones with radioactive carbon, this problem could be solved in a short time, since selective absorption would be demonstrable immediately by a rise in the radioactivity of the reactive end organ (uterus, for example) as compared with other bodily tissues. Were such a localization of radioactive hormone demonstrable, the possibility of applying this activity therapeutically becomes apparent immediately. Carcinoma of the thyroid and hyperthyroidism have been treated successfully with artificially radioactive iodine because this element becomes concentrated in normal and some neoplastic thyroid tissue. Were estrone made with radioactive carbon to behave similarly, a therapeutic concentration in the uterus or breast is conceivable.

Even though selective absorption of steroids does not occur, the problems of the metabolism of these substances would be enormously simplified if hormones made with radioactive carbon were available. The fate of injected substances could be followed very quickly and easily by exact physical measuring devices—

*This work was supported in part by a grant from the American Cancer Society administered by the Committee on Growth, National Research Council.

Conclusions

1. Six hundred cases having received radiation therapy to the pelvic area for malignancies are reviewed.
2. Transitory and permanent pathologic change in the rectum secondary to irradiation therapy is a common and vexing entity.
3. To insure adequate irradiation to a tumor of the pelvis certain irreversible changes must ensue.
4. Of 600 cases reviewed, there were 523 cases of radiation sickness and 70 cases which developed permanent rectal changes.
5. Onset and course of radiation sickness are unpredictable and their management grossly unsatisfactory.
6. Higher doses of radiation therapy tend to produce permanent rectal lesions earlier and of a more serious nature.
7. Radium is a more serious offender than are x-rays.
8. Factitial proctitis makes up the bulk of permanent rectal changes secondary to irradiation of the pelvis for pelvic malignancies.
9. The region of the rectosigmoid junction is most frequently involved by a factitial proctitis.
10. Onset and course of factitial proctitis are unpredictable and their management grossly unsatisfactory.
11. Colostomy is employed to check excessive bleeding or relieve obstructions. The results obtained frequently are negligible.
12. Rectal stenosis following radiation to pelvic malignancies occurred 48 times in the series of 600 cases. The process is irreversible.
13. One case of fibrosis without stricture was encountered.
14. Rectovaginal fistula developed in 13 patients, in this series. Spontaneous closure occurred in two cases.
15. Rectovaginal fistula occurs secondarily to metastatic invasion of the bowel and devitaliation of tissue in the rectovaginal septum.
16. Secondary carcinoma of the bowel occurred in 10 cases. One primary adenocarcinoma of the rectum developed in a case of squamous-cell carcinoma of the cervix.

amount of equilin used was 10 to 20 per cent in excess of that theoretically necessary to combine with all the bromine present in the sodium bromide. The receiving tube was cooled in an ice-water bath. The course of the reaction was followed by the use of a portable electroscope. Most of the radioactive material was found to be in the receiver after one to one and one-half hours.

The chloroform solution was transferred to a 50 ml. separatory funnel and the chloroform layer was withdrawn from the water which had condensed in the receiver during the bromine distillation. The chloroform solution, containing dibromestrone, was washed twice with 10 ml. portions of water to remove any hydrobromic acid which might be present. Practically all of the activity stayed in the chloroform which then was evaporated to dryness.

When this was carried on slowly, rosettes of white or colorless needlelike crystals were found to form on the bottom of the evaporating beaker. These crystals contained enough bromine to indicate complete bromination of 83 per cent of the equilin.*

The dry crystals were dissolved in warm absolute alcohol in which they were freely soluble. Before injection into experimental animals, the alcoholic solution was added to four times its quantity of distilled water, making a 20 per cent alcoholic solution. A very finely dispersed white precipitate of hormone formed at once, settling to the bottom of the solution in the course of an hour's standing. The experimental animals were injected intravenously with this material, either immediately after it had been made up or following thorough agitation to insure a uniform suspension. A certain amount of the watery suspension of the hormone was kept apart to serve as a standard in determining percentage bromine recoveries with the Geiger counter.

Dibromestrone was injected into twelve rabbits, one monkey and two dogs. One rabbit was injected with sodium bromide alone. The experiments were done with the purpose of answering two questions: first, was the hormone concentrated in any particular organ, and, second, by what route and in what quantities was it excreted?

In the rabbits, either entire organs or parts of them were removed, weighed, and dissolved by boiling in 5 c.c. of 10 per cent solution of potassium hydroxide. The purpose of this was to obtain uniform solutions for the measurement of radioactivity by Geiger counter. Obviously when one's measurements depend on the number of β particles or γ rays reaching a particular spot, it is imperative that all samples should be in the same volume, at the same distance from the counter tube, and, if in liquid form, dissolved in the same solvent. The organs used were uterus, ovaries, testes, spleen, liver, kidney, adrenals, and gall bladder. Counts were made also on the blood, urine, and various parts of the intestines.

A female monkey was injected intravenously with dibromestrone and killed 24 hours later. The uterus, ovaries, gall bladder, and a piece of liver were dissolved in potassium hydroxide and their radioactivity measured.

A female dog, injected with the material, was used primarily to study the rate of excretion of the steroid in the bile, but, after the animal had been killed six hours after injection of the steroid, the uterus was removed, dissolved in potassium hydroxide, and measured in the Geiger counter.

The second problem, i.e., the routes of excretion of the steroid and the rates at which this occurred, was studied first by killing the injected rabbits at varying intervals, one-half hour, two hours, six hours, 24 hours and 37 hours. Measurements were made of the radioactivity of the urine and of the feces in the small bowel, cecum, and large bowel, at varying intervals. It became apparent very

*Analysis by Wm. Saschek.

the Geiger counter, electroscope, tissue radioautographs, etc., rather than by the uncertain applications of steroid and colloid chemistry, combined with the many inaccuracies and time-consuming techniques of biologic testing.

Obviously, radioactive testosterone, progesterone, and estrone are urgently needed to unlock the mysteries of steroid metabolism and for their possible therapeutic applications. But, up to the present time, no such substances have been synthesized* and the problems of such synthesis appear to be very complex. A possible short-cut in this difficulty appeared in the suggestion that one of the steroids might be treated successfully with an artificially radioactive halogen such as bromine. It was thought that the brominated steroid might behave in a fashion sufficiently similar to the parent hormone so that conclusions could be drawn in these questions of selective absorption and routes and methods of metabolism.

After some discussion the substance "equilin" was chosen as a starting compound, since, as will be seen by a glance at Fig. 1, bromination of the double bond in the B ring leads to the formation of "dibromestrone," a substance differing from estrone only in having two atoms of bromine in the positions occupied by two atoms of hydrogen. At the present time pure equilin is more difficult to get than is radioactive bromine.**

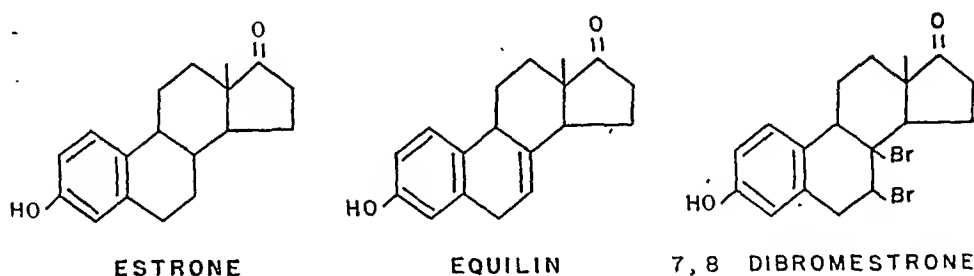


Fig. 1.

Methods

Bromine 82, a radioactive isotope of bromine with a half life of 32 hours, was obtained in the form of sodium bromide in aqueous solution from the cyclotron of Columbia University. In general, the quantities available were in the neighborhood of 2 to 4 mg. of sodium bromide, the radioactivity of which varied from $1\frac{1}{2}$ to 10 mc. (0.6 to 3.26 mc. per mg.). As received from the physical laboratory at the cyclotron, the sodium bromide was dissolved in 100 to 200 ml. of water. This excess of water was removed by boiling under a hood until the solution had been concentrated to 3 to 5 ml. The sodium bromide solution was added to an oxidizing mixture consisting of 1 Gm. of manganese dioxide and 3 ml. of concentrated sulphuric acid. The test tube containing the mixture was heated gently with a microburner and the bromine generated was carried over into a 12-inch test tube containing equilin dissolved in 20 ml. of chloroform by flushing the boiling oxidizing mixture with a slow stream of nitrogen. The

*Since this article was submitted, a method of synthesizing radioactive testosterone has been described by R. B. Turner in *Science* 106: 248, Sept. 12, 1947.

**We wish to thank Dr. Oscar Wintersteiner for being so generous as to supply us with the equilin we have used in these experiments.

TABLE I. RABBIT NO. 3, KILLED SIX HOURS AFTER INTRAVENOUS INJECTION OF HORMONE EMULSION

| | COUNTS PER MINUTE ABOVE BACKGROUND | PER CENT OF TOTAL HORMONES INJECTED |
|---|--|---|
| Blood | 29 | |
| Spleen | 16 | |
| Adrenals | 5 | |
| Ovaries | 0 | |
| Uterus | 10 | |
| Liver (Sample measured, 2.263 Gm.) | 116 | |
| Liver (total organ, calculated) | 3,828 | 1.2 |
| Gall bladder | 7,608 | 2.5 |
| Kidney (Sample measured, 4.06 Gm.) | 612 | |
| Kidneys (Total, both, calculated) | 2,264 | 0.7 |
| Urine (1 c.c. measured) | 6,208 | |
| Urine (Total, 8 c.c., calculated) | 49,664 | 16.0 |
| Small bowel (Sample measured) | 280 | |
| Small bowel (total, calculated) | 5,600 | 1.8 |
| Cecum (Sample measured) | 904 | |
| Cecum (Total, calculated) | 36,160 | 12.0 |
| Large bowel (Sample measured) | 1,432 | |
| Large bowel (Total calculated) | 32,936 | 10.9 |
| Total hormone in bowel and bowel contents | | 24.7 |

That these observations are not unique and peculiar to this one animal is borne out by our other findings, which will not be detailed here. The uterus invariably contained very small quantities of bromine, no matter whether the interval between injection and killing the animal was thirty minutes, two hours, six hours, or thirty-seven hours. The distribution of bromine was essentially the same, though total quantities were considerably smaller in the animal injected subcutaneously. The amount of bromine found in the urine as compared with that in the gastrointestinal tract varied somewhat from animal to animal. In general, about 40 to 50 per cent of the bromine given as dibromestronc intravenously appeared in the urine or feces in two to six hours. In Rabbit No. 2, 14.4 per cent was in the urine, 25.8 per cent in the feces two hours after injection. In Rabbit No. 4, 38.4 per cent was in the urine and 12.5 per cent in the feces. Two male rabbits showed no bromine concentration in their testes.

Measurements made on one female monkey were not so detailed but, again, showed marked concentration of radioactive bromine in the gall bladder and very little in the uterus. The counts above background were uterus 8, ovaries 20, 4.2 Gm. of liver 24, and gall bladder 1,484.

One female dog used for studying the excretion curve of bromine in the bile showed less than 1 per cent of bromine in the uterus.

We may conclude, then, that radioactive dibromestronc is not selectively absorbed by the uterus, ovaries, testes, or adrenals of rabbits or by the uterus of the dog or the monkey.

2. *Excretion Route of Dibromestronc.*—The second question, as to the route or routes of excretion of this substance, seemed plain from the findings in kidney, urine, liver, gall bladder and bowel. To study this aspect further, counts were made on small intestine, cecum, and large intestine of rabbits killed thirty minutes, two hours and six hours after intravenous injection. In the thirty-minute rabbit, relatively high counts were found in the kidney and liver and particularly in the small intestine. The gall bladder showed little or no activity. Evidently the steroid had been poured down through the common duct into the bowel and had not as yet backed up into the gall bladder. At two hours, 21.5 per cent of the injected material was in the small bowel, 4.5 per cent in the

soon that the principal route of excretion was through the bile into the intestine. Consequently, in one rabbit, the alcoholic steroid was injected directly into the gall bladder and its appearance in the urine studied. In another, the common bile duct was ligated and the effect of this procedure on the radioactivity of the urine and feces obtained. While most of the animals were given the radioactive dibromestronc intravenously, one animal was injected subcutaneously to see if this changed the subsequent distribution of the radioactive material.

Finally, two experiments were performed on dogs anesthetized with Nembutal and morphine, in which the common bile duct was exposed and a No. 8 soft rubber catheter inserted into it, so that samples of bile and urine could be obtained at fifteen-minute intervals after injection of the steroid.

The measurements* were carried out, for the most part, inside a lead tank to insure protection of the counting tube from stray ionizing radiation. Such an apparatus does not stop a constant background from cosmic rays or penetrating gamma radiation, but this background has been subtracted from the reading obtained in each case. Since potassium is itself weakly radioactive, the counts due to the potassium hydroxide alone were determined and subtracted also.

Finally, a word should be included about the extraordinary sensitivity of the method. The quantities of radioactive bromine injected into the animals were often less than half a millieurie, the quantities of steroid less than one milligram, yet the detection of as little as 3/1000 of the total amount of injected bromine in an individual sample or organ was easy and accurate.

Results

1. *Localization of Injected Dibromestronc in the Animal Body.*—Since radioactive dibromestronc was limited in quantity because of the rarity of equilin and the difficulty of getting Bromine S2, an attempt was made to answer as many questions as possible with a few experimental animals. While organs from ten rabbits were assayed for their content of radioactive bromine, the measurements obtained are not strictly comparable since the amounts of hormone injected, the quantities of Bromine S2 used in each case, and the times between injection and the death of the animal varied. Also, in one animal, the common bile duct was ligated, in another the hormone was injected into the gall bladder, in a third, a deep ether anesthesia was given before the injection of the hormone, while a fourth had the hormone given subcutaneously. Obviously, to group all the measurements together would be meaningless, while to give all the experimental data would be confusing.

Perhaps the best way to answer the first question as to the localization of dibromestronc after injection is to give in detail the figures for one animal, Rabbit No. 3, and this is done in Table I. If one peruses the figures in Table I, it becomes apparent at once that six hours after intravenous injection of a finely divided dispersion of dibromestronc, the amount of bromine found in the blood, spleen, adrenals, ovaries, and uterus is negligible. Considerable quantities, on the other hand, are found in the kidneys, 0.7 per cent. the liver, 1.2 per cent, and particularly in the gall bladder, 2.5 per cent. The later observations led to measurements on the urine, where 16 per cent of the entire injected bromine was found, and measurements on samples of hydrolyzed bowel with its fecal contents. The total amount in the gastrointestinal tract was 24.7 per cent, most of this in the cecum and large intestine.

*All counts were made in the laboratories of the Department of Radiological Research under the guidance of Dr. Edith Quimby, whose cooperation we wish to acknowledge with gratitude.

the bowel for reabsorption. These observations would seem to confirm strongly the theory that there is an enterohepatic or portal circulation of this particular steroid.

The bile collected from the two dogs was examined to see whether the bromine could be extracted with ether. Again, as with the urine, this was not found to be the case. The bromine went into the ether phase when the bile was shaken with equal quantities in a separatory funnel only after hydrolysis with hydrochloric acid. Seventy-seven per cent was ether soluble. Of this material, 89 per cent was soluble in 2 normal sodium hydroxide.

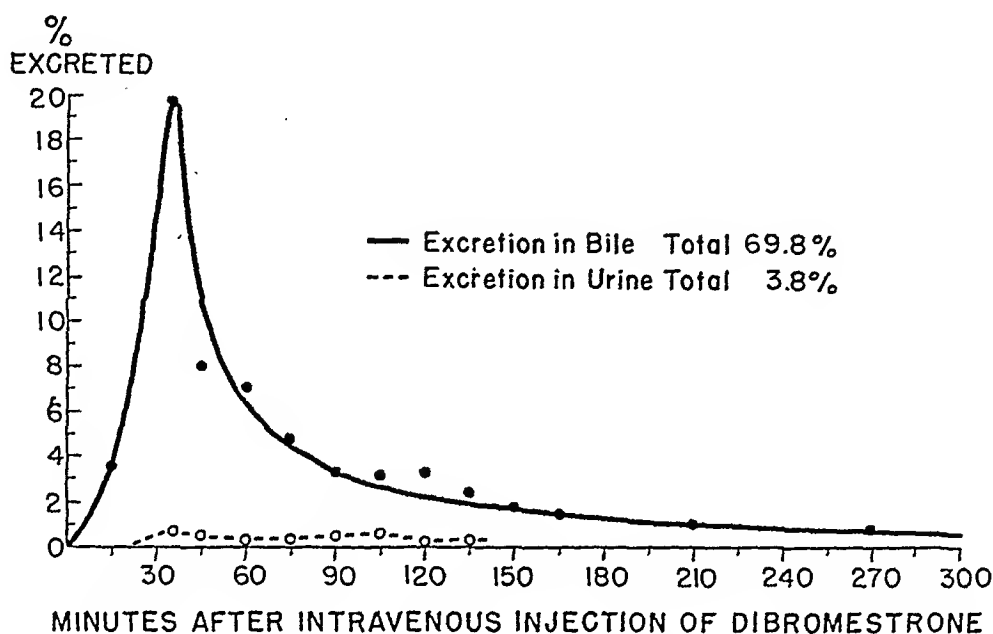


Fig. 2.—Excretion of dibromestronone in a female dog.

Discussion

Adding bromine to estrone, as we have done, destroys most, if not all, of its estrogenic properties. This fact was known before the experiments recorded above had been performed, the material being tested out on six infantile female rats. Some increase in uterine weight was recorded, but this was so slight as to be accounted for probably by unbrominated equilin. In spite of this lack of estrogenic potency, it still seemed reasonable to look for localization of such a steroid, so closely related to estrone, in the genital tract. Since none was found, the question of localization in the case of the naturally occurring hormones or other actively estrogenic chemicals must await further investigation, possibly with radioactive carbon as one of the building blocks in the natural hormone itself.

The findings reported in this paper seem to support strongly the contentions of Cantarow et al.^{3, 4} that large quantities of injected estrogens may be recovered from the bile. There seems to be considerable doubt as to what proportion of such steroids are present in the bile, Cantarow originally reporting a recovery of 34 to 64 per cent in the first twenty-four hours and almost all the remaining injected estrogens in the subsequent forty-eight hours. A subsequent paper by

cecum, and only 0.8 per cent in the large intestine. By six hours, most of the activity was found in the cecum, 12 per cent, and the large intestine, 10.9 per cent, and only 1.8 per cent in the small bowel.

Not only is the steroid excreted into the bowel through the bile, but it can be reabsorbed from the bowel and transported to the kidney, as proved by the injection of the material in one animal into the gall bladder.

Perhaps of particular interest in this case is the finding that the steroid was excreted very probably as a conjugated phenolic steroid. At least, the material found in the urine of this animal was not ether soluble until after hydrolysis. When the 15 c.c. of urine found in its urinary bladder had been boiled in a flask fitted with a reflux condenser for thirty minutes with 5 c.c. of concentrated hydrochloric acid, 84 per cent of the radioactive bromine could be extracted by shaking with ether. This material was insoluble in sodium bicarbonate, but was completely extracted with normal sodium hydroxide. These properties certainly fit with the concept that radioactive dibromestronone can be absorbed as such from the bowel, conjugated with an organic acid such as glucuronic acid, and then excreted into the urine without damage to the phenolic steroid structure of the substance and without liberation of the attached bromine.

That the biliary pathway of excretion is not necessary for the body to rid itself of this substance was shown in an animal in which the common bile duct was ligated. This procedure is apparently fatal in a day or so to the rabbit, as was proved by a preliminary experiment. The appearance of the urine of the experimental animal was thick and brown, but, again, the bromine in it could not be extracted with ether before hydrolysis. Eighty-six per cent was removed by shaking with ether after one-half hour's hydrolysis. Of this material, 22 per cent was soluble in sodium bicarbonate, the rest in normal sodium hydroxide. Again, this suggests that the steroid was present in the urine chiefly as a conjugated phenolic steroid. Similar extraction properties were noted in experiments on the material found six hours after injection in the urine of a rabbit that had not been operated upon.

An attempt was made to study the nature of the bromine-containing substances in the feces of injected rabbits. Manipulations to extract watery solutions of rabbit feces with ether were most unsatisfactory. Shaking such solutions results in the formation of very stable emulsions, some approaching the character of jells. Exploration of these materials with the counter seemed to show the active bromine in the emulsion rather than in any watery solution that could be separated from it. However, this might be due to absorption of steroid on the particles of the emulsion, or it is not beyond the bounds of possibility that steroids excreted as conjugated glucuronides are broken up in the bowel and exist there as free steroids.

The last two experiments were acute ones performed upon dogs to determine the excretion rate of dibromestronone in the bile. The first of these was not entirely satisfactory, since a concomitant collection of urine was not carried out (male dog) and some trouble was experienced in measuring the radioactivity of the uninjected standard. The observations were made, however, that all bromine had left the blood within fifteen minutes of the time of injection and that excretion was prompt in the bile, reaching a peak sometime between one hour and one and three-fourths hours after intravenous injection.

The observations made on the second dog are recorded in Fig. 2. The prompt rise in excretion rate to a peak at thirty minutes and its fall to very low levels at the end of four hours are worth noting. Also remarkable are the large excretion rate in the bile, 69.8 per cent in five hours, and the small amount of bromine found in the urine, about 4 per cent, when the bile is not returned to

Summary

1. Equilin has been brominated with radioactive Bromine 82 to give dibromestrone.
2. This material is weakly estrogenic, if at all.
3. Dibromestrone is not selectively localized in the rabbit in the adrenals, spleen, uterus, ovary or testis. A high concentration occurs in the gall bladder within six hours after injection.
4. Dibromestrone is not selectively localized in the liver, ovaries, or uterus of the female monkey or in the uterus of the dog.
5. It is largely excreted through the common bile duct into the intestine. From this organ it may be reabsorbed into the portal circulation, ultimately to find its way to the kidney and into the urine.
6. Solubility tests are consistent with the hypothesis that dibromestrone is excreted into the bile and into the urine largely as a conjugated phenolic steroid.
7. These observations strongly support the theory of an enterohepatic circulation of dibromestrone and, by implication, of other steroids as well.

The authors wish to acknowledge with gratitude the technical assistance of Dr. Equinn Munnell in performing the bile fistulas on dogs and of Miss Charlotte Schmidt in making many of the Geiger counter measurements.

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Pearlman, Pasehki, Cantarow, et al.¹² reduced this to 10.4 per cent. Longwell and McKee¹¹ report a total recovery of 1.3 to 8 per cent of injected estrone from the bile in bile fistula dogs.

The substances reported by Cantarow and his co-workers were thought to be largely unconjugated, but this seems to have been largely determined by the injection of diluted unfractionated bile directly into the assay animals. The results of Longwell and McKee were based on animal assays also. One cannot help wondering whether the diversity of results here is not due to methods of biologic assay, and variations in the way the bile was hydrolyzed. If our own observations are correct, and can be applied to estrone, the steroids are excreted as water soluble conjugates. If these substances are glucuronides, as has been widely assumed, they have much less biologic activity than their parent steroids. Cohen, Marrian and Odell,⁵ for instance, found estriol glucuronide to be only 1/29th as active biologically as estriol. Schapiro¹³ reports similar findings for estradiol glucuronide. Hydrolysis may break up these esters but destroy part of their biologic activity at the same time.

The advantage of using a radioactive steroid is that questions of hydrolysis, or conjugation, interfering with biologic potency have no effect on the physical potency, the radioactive content of the tissues or fluids being measured. Whether the steroid is conjugated or unconjugated, the Geiger counter detects the presence of the radioactive material just the same, and the only problem is to make sure that this radioactivity is still part of a steroid nucleus. The data we have given above would seem to us almost to prove that dibromestron, at least, is excreted in large quantities through the bile in a water soluble form and that it is partly reabsorbed and re-excreted both through the bile and through the kidney into the urine.

Several observations suggest that this may be true of the natural hormones too. The experiments of the Biskinds,^{1, 2} showing that implantation of testis or ovary in the portal circulation frees the rest of the body from any steroid influence that they might exert, is one. Years ago, in 1928, Dohrn and Faure⁶ found 300,000 mouse units of estrogenic activity per kg. of dried feces from pregnant women. In 1930, Siebke and Schuschania¹⁴ assayed urine and feces during an entire monthly cycle in three normal women. They found considerable quantities of estrogens in the feces, though, in general, somewhat less than in the urine. Recently Levin⁹ has found that pregnant cows excrete little estrogen in their urine, but 5,000 to 10,000 rat units per kg. of dry feces.

If it can be proved that an enterohepatic circulation plays a large role in the metabolism of all the body steroids, as it does with dibromestron, urinary assays of these substances, both qualitative and quantitative with respect to disease, become of little significance, since the physiological state of the liver, the enzymes and motility of the small intestine, and the intestinal flora of the large intestine may play major roles in the final product issuing from the kidneys. Unless these factors can be controlled rigidly, the interpretation of the significance of new steroids or abnormal steroid patterns would be hard indeed.

in regard to (a) the number of hours preceding the first evidence of histologic change, (b) the extent of the follicular reaction, (c) the time necessary for its appearance ("lag-time"), and (d) the duration of the action.

Materials and Methods

Fifty-five patients, ranging in age from 27 to 85 years, served as subjects in the present investigations. Seven of the total number were tested at various times with each of two estrogenic materials; one was tested with three, one with four, and one with five different preparations. There was thus a total of 71 test cases.

TABLE I. NATURE AND AMOUNTS OF ESTROGENS TESTED

| DRUG | ADMINISTERED | |
|---|--------------------|-----------------|
| | AMOUNT (IN MG.) | NUMBER OF CASES |
| 1. Estradiol in sesame oil | 1 | 3 |
| Estradiol in sesame oil | 2 | 3 |
| Estradiol in sesame oil | 3 | 3 |
| 2. Estradiol in propylene glycol | 1 | 3 |
| Estradiol in propylene glycol | 2 | 3 |
| 3. Estradiol dipropionate in sesame oil | 1 | 19 |
| Estradiol dipropionate in sesame oil | 2 | 5 |
| Estradiol dipropionate in sesame oil | 5 | 3 |
| 4. Estradiol benzoate in peanut oil | 1 | 8 |
| 5. Estradiol benzoate in propylene glycol | 1 | 3 |
| Estradiol benzoate in propylene glycol. | 2 | 5 |
| 6. Estradiol (1 mg.) and estradiol benzoate (1 mg.) in sesame oil | 2 | 4 |
| 7. Estradiol benzoate (1 mg.) and estradiol (0.5 mg.) in propylene glycol | 1.5 | 4 |
| Estradiol benzoate (1 mg.) and estradiol (0.5 mg.) in propylene glycol | 3 | 5 |

Seven preparations of the hormone were used.* These are tabulated below to indicate the specific type of estrogen, the menstruum, the amount used in each test case, and the number of patients tested with each drug.

Vaginal smears were obtained daily from each subject for a period of several days prior to injection of the hormone in order to determine the normal type of smear in each individual. A sterile Becton, Dickinson Asepto syringe was inserted into the posterior fornix of the vaginal canal and a small amount of vaginal fluid was withdrawn. This was expressed on to a clean glass slide and spread thinly. The material was fixed immediately in a mixture of equal parts of ether and 95% alcohol. A number of slides were stained in accordance with the technique outlined by Papanicolaou¹¹; the remainder were treated with the P.G.I. stain.⁴

In each instance a single injection of the hormone was given. Following this injection vaginal smears were taken at twelve-hour intervals, over periods of time ranging from 60 to more than 360 hours. Each smear was stained as above detailed and tabulation made of cornified cells, superficial cells, intermediate cells, basal cells, leucocytes, erythrocytes, bacteria, amount and character of mucus, clarity and degree of follicular reaction. The principal features of the smear characteristic of the follicular reaction are the relative percentage of cornified cells, the degree of clarity and the relative number

*The estrogenic preparations used in this study were furnished by Dr. Edward L. Henderson of the Schering Corporation, Bloomfield, N. J. His courtesy is herewith gratefully acknowledged.

EFFECTS OF VARIOUS ESTROGENIC PREPARATIONS ON THE VAGINAL MUCOSA

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MANY preparations having ovarian follicular hormone activity are now marketed; numerous others are in process of manufacture. Several factors make it difficult to appraise fully their relative therapeutic merits. For instance, some are standardized by weight; others in international units, and still others in mouse or rat units. It is almost impossible to translate the full activity of one in terms of the other, as the methods employed in the standardization vary somewhat from firm to firm. Moreover, when the rat unit is used, its bioassay value, in terms of international units, as employed by one manufacturer, may be a fraction, or a multiple, of that used by a second.

Further difficulties arise in the selection of an estrogen, when we realize that the influence of the route of administration, the chemical state of the estrogen (e.g. whether free or conjugated), and the menstruum in which it is carried may alter the speed and degree of activity exhibited. Finally, there is no assurance that species differences in effects do not occur, so that the "best" estrogen for the rat or other small animal may not necessarily exert optimum follicular hormonal activity in the human being.

On what basis, then, shall we choose our estrogen? The evaluation of subjective symptoms and their course under therapy is frequently difficult. No very satisfactory objective method exists which is readily applicable for day-to-day follow-up in each individual patient. However, several approaches have been made to the problem experimentally, with the hope, at least, of obtaining some data concerning the rapidity, degree, and duration of action in mankind. Among these must be included withdrawal bleeding time,^{1, 3, 18} estimation of urinary estrogens and gonadotropins,^{3, 14} studies of alterations in cervical mucus^{3, 7} and comparison of vaginal smears taken prior to and during the administration of a hormone.^{2, 5, 8, 12, 15, 17} Correlation of the results of vaginal smear examination with basal body temperature,¹³ or with endometrial biopsies,⁶ has also been attempted. Of these, the vaginal smear lends itself most readily to multiple and continuous observations. For this reason it was chosen for the present investigation. In order to eliminate an ovarian influence, insofar as possible, surgically castrated and postmenopausal women were used with few exceptions. By this method we have been able to observe the results of *single* injections of various preparations upon the vaginal mucosa

TABLE III. "LAG-TIME" AND DURATION OF FOLLICULAR REACTION FOLLOWING A SINGLE INJECTION OF VARIOUS ESTROGENIC PREPARATIONS

| NUMBER OF CASES SHOWING A FOLLICULAR REACTION | DRUG | MENSTRUUM | DOSE (MG.) | APPROXIMATE "LAG-TIME" (HOURS) | | APPROXIMATE DURATION OF FOLLICULAR REACTION (HOURS) | |
|---|--|------------------|------------|--------------------------------|-----|---|--------------|
| | | | | RANGE | AV. | RANGE | AV. |
| 2 | Estradiol | Sesame oil | 1 | 96-120 | 108 | 24-48 | 36 |
| 3 | Estradiol | Sesame oil | 2 | 95-107 | 101 | 12-200* | 88 (approx) |
| 2 | Estradiol | Sesame oil | 3 | 53-101 | 77 | 42-134 | 89 |
| 3 | Estradiol | Propylene glycol | 1 | 108-132 | 116 | 108-132 | 116 |
| 2 | Estradiol | Propylene glycol | 2 | 120-180 | 150 | 12-132 | 72 |
| 3 | Estradiol dipropionate | Sesame oil | 1 | 60-120 | 88 | 30-159 | 100 (approx) |
| 5 | Estradiol dipropionate | Sesame oil | 2 | 77-95 | 87 | 108-198 | 143 |
| 3 | Estradiol dipropionate | Sesame oil | 5 | 42-80 | 67 | 96-168* | 138 (approx) |
| 4 | Estradiol benzoate | Peanut oil | 1 | 60-108 | 93 | 30-138 | 82 |
| 1 | Estradiol benzoate | Propylene glycol | 1 | 120 | | 24 | |
| 3 | Estradiol benzoate | Propylene glycol | 2 | 72-108 | 87 | 60-204 | 132 |
| 4 | Estradiol benzoate 1 mg. & estradiol oil 1 mg. | Sesame oil | 2 | 84-90 | 88 | 24-138 | 94 |
| 4 | Estradiol benzoate 1 mg. & Estradiol 0.5 mg. | Propylene glycol | 1.5 | 72-120 | 102 | 60-120 | 99 |
| 5 | Estradiol benzoate 1 mg. & Estradiol 0.5 mg. | Propylene glycol | 3 | 60-120 | 95 | 96-200* | 142 (approx) |

*Follicular reaction persisting at time of discharge from hospital.

Following a dose of 1 mg., the shortest lag-time appeared in a 68-year-old woman who had received estradiol benzoate in peanut oil. For the 1.5 mg. dosage level, the most rapid response occurred in a woman aged 53, who received 1 mg. of estradiol benzoate plus 0.5 mg. estradiol in sesame oil. The most prompt reaction seen subsequent to the administration of 2 mg. of hormone appeared in a 44-year-old subject who had been injected with 2 mg. of estradiol benzoate in propylene glycol. Among subjects who received 3 mg. of estrogen, the earliest follicular reaction was noted in one 50-year-old woman who had received 2 mg. estradiol benzoate plus 1 mg. estradiol in sesame oil. After a lapse of several weeks, injection of 3 mg. of estradiol in sesame oil was given to this same subject. While the follicular response occurred rapidly, it was not as rapid as with the preceding injection of the estrogen mixture. The shortest lag-time observed in all test subjects was in the case of a 52-year-old woman who received an injection of 5 mg. of estradiol dipropionate in sesame oil. Fig. 1 shows the average lag-time for each test case in relation to specific

of leucocytes. Estrogenic activity and the amount of cornification can be directly correlated in the normal woman of childbearing years. Cornification, therefore, served as the major index in estimating the effectiveness of the dose. Follicular reaction was recorded in grades represented by 0 to 4 plus. Cornified cells, ranging from approximately 10 to 25% of the total number of cells in the smear, constituted a 1 plus reaction; 25 to 50%, a 2 plus reaction, 50 to 75%, a 3 plus reaction, and 75% or more a 4 plus reaction. To a certain extent, all of these factors had to be reconciled with those in control smears. For example, a smear of the premenstrual type will frequently contain a small to moderate number of cornified cells; a smear of the pseudoleucopenic type is normally devoid of leucocytes.

Results

Types of Normal Smears Observed in Postmenopausal Women.—Smears of the postmenopausal women were divided into groups (Table II) according to the classification of Papanicolaou and Shorr¹²: (1) premenstrual, (2) intermediate, (3) atrophic (or menopausal-atrophic), (4) pseudoleucopenic, (5) mucus, (6) *B. vaginalis*. It was not possible to categorize correctly the smears of 2 subjects who, while still in the childbearing age, had definite menstrual disturbances.

TABLE II. TYPES OF VAGINAL SMEARS OBSERVED IN 55 PATIENTS OF VARYING AGES

| SMEAR TYPE | NUMBER OF SUBJECTS IN EACH AGE GROUP | | | | | | |
|------------------|--------------------------------------|-------|-------|-------|-------|-------|-------|
| | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80-89 |
| Premenstrual | 1* | | 3 | 3 | | | |
| Pseudoleucopenic | | | 1 | 6 | 5 | 1 | |
| Intermediate | | | 1 | 4 | 4 | 1 | 1 |
| Mucus | | | 3 | 3 | 2 | 4 | 1 |
| Atrophic | | | 1 | 3 | 5 | | |
| Unclassified | | 2†‡ | | | | | |
| Total | 1 | 2 | 9 | 19 | 16 | 6 | 2 |

*Surgical Menopause.

†Amenorrhea.

‡Sterility.

The Period of Observation Following Injection of the Estrogenic Preparation.—In the early part of our investigation, patients were observed for a period of sixty hours only. Of 16 patients so studied, only one, at the end of sixty hours, gave evidence of a follicular reaction and one showed no change whatsoever. In the smears of the remaining 14, there was an increased clarity, a decrease in the number of leucocytes, and a change from immature or basal types of cells to those of a more advanced, or superficial type. On the basis of these findings the period of observation was extended. It was subsequently noted that a follicular reaction was preceded in all instances by alterations in the smear similar to those just mentioned.

Dosage and "Lag-Time."—"Lag-time" is defined as the number of hours between injection of the hormone and the appearance of a follicular reaction. The range of lag-time in patients receiving an injection of 1 mg. of estrogenic substance was 60 to 120 hours. In patients who were given 1.5 mg. it was 72 to 120 hours, and in the subjects who received 2 mg., 72 to 216 hours. In the instances where an injection of 3 mg. was given, lag-time was 53 to 120 hours, and in patients who had an injection of 5 mg., this period ranged from 42 to 80 hours. (Table III; Fig. 1.)

estradiol dipropionate in sesame oil elicited a true follicular reaction; however, alterations of cell type occurred more rapidly following injection of the former preparation.

Dosage and Degree of Follicular Reaction.—Among the 71 test cases, the vaginal smears of three evidenced no changes whatsoever. Each of two of these, 66 and 71 years of age, respectively, had been injected with 1 mg. of estradiol dipropionate in sesame oil and had been observed periodically through sixty hours. The third patient, 53 years old had received 1 mg. of estradiol in sesame oil and had remained under surveillance for a period of 220 hours.

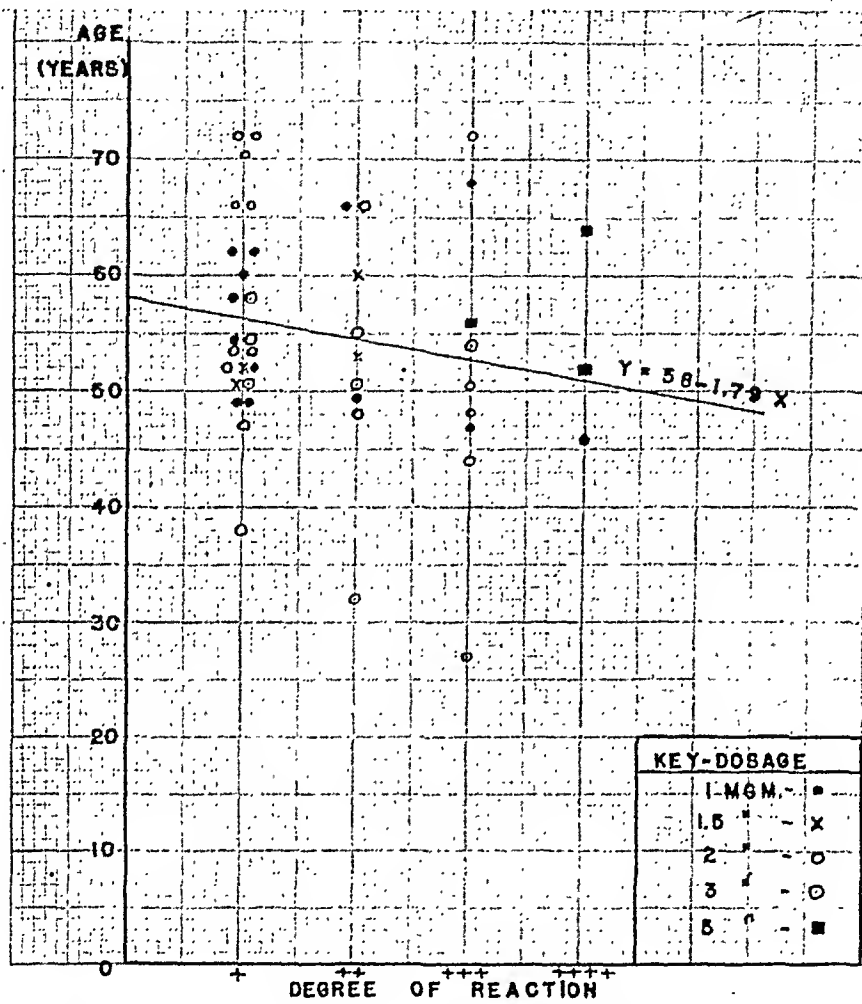


Fig. 2.—The relation of age to the degree of follicular reaction as determined by 44 tests.

In 24 of the remaining 68 tests a follicular reaction was not obtained although the vaginal smears showed definite changes; thirteen of these were watched for sixty-hour periods, only.

The incidence of the degree of response, graded from one to four plus, varied as follows: one plus in 23 test subjects with a range of age from 38 to 72 years; two plus in 9, who were from 32 to 66 years old; three plus in 9, who were between 27 and 72 years of age, and four plus in 3 subjects between the ages of 46 and 64 years.

Fig. 2 is constructed to show the degree of follicular reaction in relation to age and the amount of hormone injected. The degree of follicular reaction in relation to specific estrogenic preparations is recorded in Table IV.

estrogenic preparations and dosages and Table III contains data regarding the range of and the average lag-time in relation to specific estrogenic preparations.

Among the patients tested twice, the following observations may be significant: (1) The lag-time following an injection of 1 mg. estradiol benzoate plus 1 mg. estradiol in sesame oil was less than that which followed an injection of 2 mg. estradiol in sesame oil. (2) The speed of reaction following an injection of 2 mg. estradiol benzoate plus 1 mg. estradiol in propylene glycol was greater than that which occurred after an injection of 3 mg. estradiol in sesame oil. In both instances, nearly equivalent amounts of hormone were used.

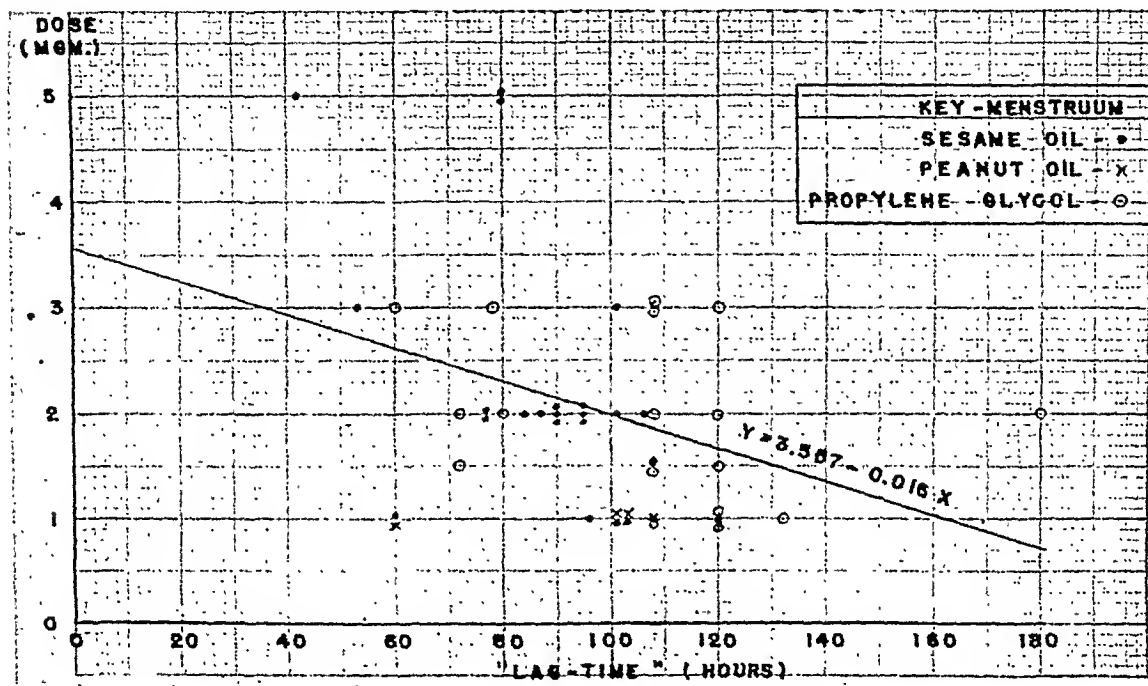


Fig. 1.—The relation of dosage and "lag-time" as determined by 44 tests.

In four cases, an injection of 2 mg. of estrogen resulted in a shorter lag-time than an injection of 1 mg. of estrogen. One patient received two injections of 1 mg. estradiol benzoate in peanut oil and was observed for periods of 60 and 264 hours, respectively. During the longer period of observation a response to the hormone was observed. A shorter lag-time was noted, however, in this subject following the larger injection of 1 mg. estradiol benzoate plus 0.5 mg. estradiol in propylene glycol.

One subject was tested with four preparations. In her, 2 mg. estradiol dipropionate in sesame oil evoked the most rapid response. The next most effective preparation was 2 mg. estradiol in sesame oil. Two mg. of estradiol in propylene glycol acted more rapidly on the vaginal mucosa than 1 mg. of estradiol dipropionate in sesame oil. Five preparations were tested on another subject; the follicular reaction which followed an injection of 5 mg. estradiol dipropionate in sesame oil was very prompt. The lag-time after an injection of 2 mg. estradiol in sesame oil was shorter than that observed following an injection of 1 mg. estradiol benzoate together with 0.5 mg. estradiol in propylene glycol. Neither an injection of 2 mg. estradiol in propylene glycol nor one of 1 mg.

in which the presence of a few cornified cells may be demonstrated, is highest among those women who are 1 to 10 years postmenopausal. The atrophic type of smear, characterized by the presence of basal cells and a high leucocyte count, predominates among women of the older age groups. One patient, 27 years of age, had had a bilateral oophorectomy 4 years earlier. Her control smears were of the premenstrual type and contained scattered cornified cells. Another patient, 43 years of age, had had a bilateral oophorectomy at the age of 32; her control smears contained basal cells only. A patient, 32 years of age, who complained of amenorrhea of approximately one year's duration, belonged to the subfunctional anovulatory type of secondary amenorrhea described by Schorr.¹⁶ Control smears of the 38-year-old woman gave no evidence of an ovulatory peak (Table II).

How exact can our classification of types of vaginal smears become? Variability in the vaginal secretion includes not only the types of cells but also the amount and character of mucus and the number and appearance of the leucocytes. Indeed, prolonged study of vaginal smears has indicated the existence, at least in some climacteric women, of a "postmenopausal sexual rhythm."¹⁰

Because of the wide variation in the degree of vaginal atrophy following the menopause, the problem of classification of each individual becomes more apparent and, assuredly, the changes noted more difficult of explanation. Are they on the basis of different tempos in the regressive process? Do they depend on continued elaboration of estrogenic substances after the menopause? Do the smears of older women which do not exhibit complete atrophy indicate a lesser degree of estrogen deficiency? In any event, the variability of the histologic patterns, both in the individual and in groups of women, serves to complicate all our attempts at comprehensive interpretation.

2. *The Period of Observation.*—The 60-hour period of observation initially used was suggested by the work of Zondek¹⁹ who produced complete estrus in ovariectomized rats within 55 hours. As previously stated, the appearance in the vaginal smears of our subjects of cells of a more mature type accompanied by a diminished leucocyte count indicated that these changes actually represented an early and mild response to estrogen. It is obvious, therefore, that because of our inadequate periods of observation in some of the cases first studied, we undoubtedly missed the full effect elicited by the hormone. This was particularly well demonstrated in one patient who was injected with 1 mg. of estradiol benzoate in peanut oil on two occasions. Following the first injection she was observed for 60 hours and her vaginal smears showed alterations of cell type and a diminished leucocyte count at the end of that period. Following a second injection of the same preparation, two months later, smears taken at 12 hour intervals for 264 hours showed a one plus degree of follicular reaction, starting at the 120th hour.

3. *Lag-Time.*—In 68 of the cases studied, changes in cell type occurred between the 48th and 80th hours following injection. A definite inverse relationship existed between the size of the dose and the number of hours.

Dosage and Duration of Follicular Reaction.—The duration, in hours, of the follicular reaction at the dosage levels indicated was: 1 mg., 24 to 159 hours; 1.5 mg., 60 to 120 hours; 2 mg., 12 to 200+ hours; 3 mg., 42 to 200+ hours; and 5 mg., 96 to 168+ hours.

From Fig. 3 and Table III it is clear that the size of an effective dose varies directly as the duration of action and inversely as the lag-time. In other words, within certain limits, the larger the dose the shorter the time necessary to effect response and the longer that response will last. In Fig. 4 the duration of the follicular reaction is plotted against the age of the subject.

TABLE IV. INTENSITY OF THE FOLLICULAR REACTION

| NUMBER OF CASES TESTED | NUMBER OF CASES SHOWING A FOLLICULAR REACTION | DRUG | MENSTRUUM | DOSE OF DRUG (MG.) | REACTION | | | |
|------------------------|---|--|------------------|--------------------|----------|----|----|----|
| | | | | | 1+ | 2+ | 3+ | 4+ |
| 3 | 2 | Estradiol | Sesame oil | 1 | 1 | | 1 | |
| 3 | 3 | Estradiol | Sesame oil | 2 | 2 | | 1 | |
| 3 | 2 | Estradiol | Sesame oil | 3 | 2 | | | |
| 3 | 3 | Estradiol | Propylene glycol | 1 | 3 | | | |
| 3 | 2 | Estradiol | Propylene glycol | 2 | 2 | | | |
| 19* | 3 | Estradiol dipropionate | Sesame oil | 1 | 1 | 1 | | 1 |
| 5 | 5 | Estradiol dipropionate | Sesame oil | 2 | 2 | 2 | 1 | |
| 3 | 3 | Estradiol dipropionate | Sesame oil | 5 | | | 1 | 2 |
| 8† | 4 | Estradiol benzoate | Peanut oil | 1 | 2 | 2 | 1 | |
| 3 | 1 | Estradiol benzoate | Propylene glycol | 1 | 1 | | | |
| 5 | 3 | Estradiol benzoate | Propylene glycol | 2 | 1 | | 2 | |
| 4 | 4 | Estradiol benzoate 1 mg. & estradiol 1 mg. | Sesame oil | 2 | 3 | 1 | | |
| 4 | 4 | Estradiol benzoate 1 mg. & estradiol 0.5 mg. | Propylene glycol | 1.5 | 2 | 2 | | |
| 5 | 5 | Estradiol benzoate 1 mg. & estradiol 0.5 mg. | Propylene glycol | 3 | 1 | 2 | 2 | |

*Eleven cases in this group were observed over a 60-hour period.

†Five cases in this group were observed over a 60-hour period.

Discussion

1. *Types of Vaginal Smears Observed in Postmenopausal Women.*—Papanicolaou and Shorr observed six different types of vaginal smears in postmenopausal women. Only five of these were noted among our subjects. One type, described by them and characterized by the presence of *B. vaginalis* (Doderlein's bacillus), was not seen in the present group of cases, although this is admittedly a not uncommon inhabitant of the vaginal tract. The bacillus was observed in occasional smears of a few of the younger subjects. Inspection of Table II reveals that the percentage of the premenstrual type of smear,

Although the number of cases tested with each drug is relatively small, it appears that the lag-time of those preparations in either sesame oil or peanut oil is shorter than that of the preparation in which propylene glycol constituted the menstruum, and that, regardless of the menstruum, the esters of estradiol were more rapidly effective than estradiol. Individual records show that age in relation to lag-time is a variable factor.

It is generally conceded that sesame oil and peanut oil act as foreign bodies and are retained in situ for a longer period than propylene glycol. It is therefore difficult to explain why the hormone in these media should evidence a more rapid action.

4. *The Degree of Follicular Reaction.*—Maximal effects, or a reproduction of a "normal" ovulatory peak, were observed in two patients, 52 and 64 years of age, respectively, following an injection of 5 mg. estradiol dipropionate in sesame oil and in one patient 46 years of age (one year since cessation of menses) following an injection of 1 mg. estradiol dipropionate in sesame oil.

The degree of follicular reaction for all subjects has been previously noted and is tabulated in Table IV and Fig. 2. In the latter, one may observe that there exists an inverse relationship between age and degree of follicular reaction and that, to a certain extent, dosage and degree of follicular reaction can be directly correlated.

Again, despite the small number of cases tested with each preparation, there is an indication that the esters of estradiol, in oily media, are capable of inducing a greater degree of reaction in the vaginal mucosa than non-esterified forms in either oil or propylene glycol.

5. *The Duration of Follicular Reaction.*—A certain difficulty is involved in the determination of the end point of follicular reaction. In vaginal smears of normal menstruating women, follicular reaction culminates in the so-called ovulatory peak which is followed by a succession of changes attributed to the hormone elaborated by the corpus luteum. In our investigation, the end point is defined not as the return to the control type of smear but as a return to a smear in which there is no evidence of cornification and, in all but smears of the pseudoleucopenic type, an increase in the number of leucocytes as well. In smears of the premenstrual type, in which occasional cornified cells are noted, the end point of follicular reaction is defined as a return to a smear in which there are relatively no more cornified cells than in the control smear. In a few instances, smears taken three weeks after a single injection showed that the stimulatory effect of the estrogen upon the mucosal epithelium had not completely disappeared.

From Fig. 4 it is clear that one cannot make a comprehensive statement regarding the duration of follicular reaction in relation to the amount of hormone injected or in relation to the age of the patient. However, despite some exceptions, certain trends can be discerned: There appears to be a tendency toward an inverse relation between age and duration of follicular reaction and a direct relation between the amount of hormone administered and the duration of its action.

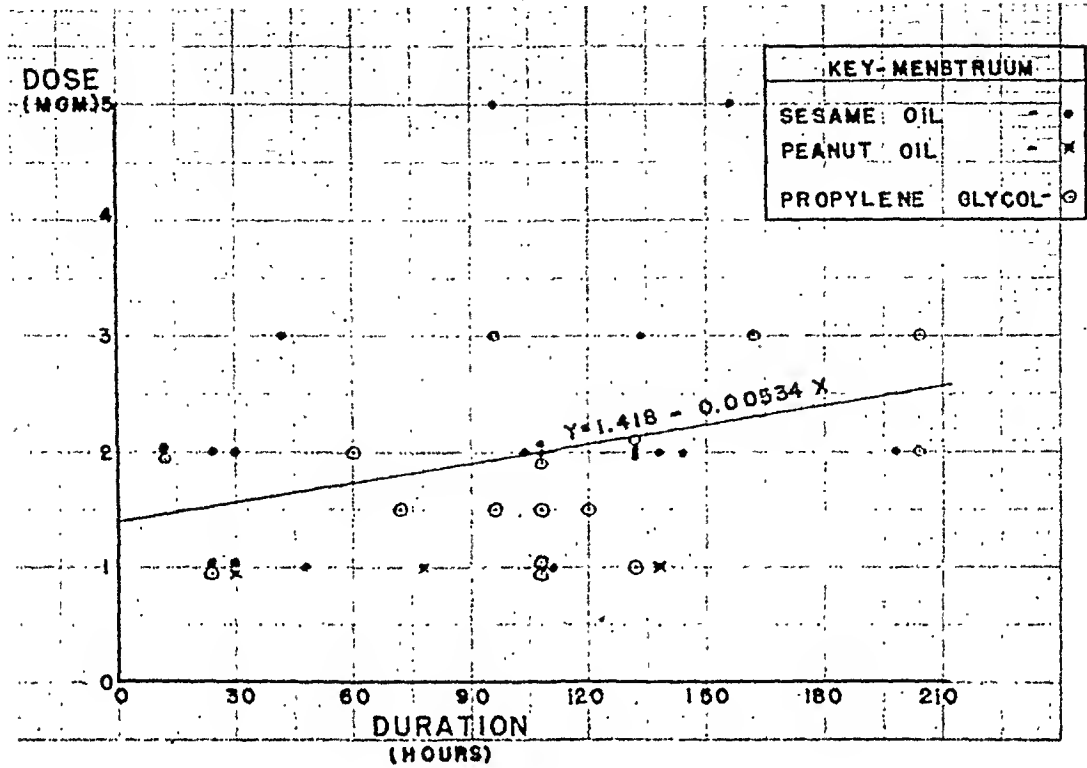


Fig. 3.—The relation of dosage and duration of follicular reaction as determined by 3S tests.

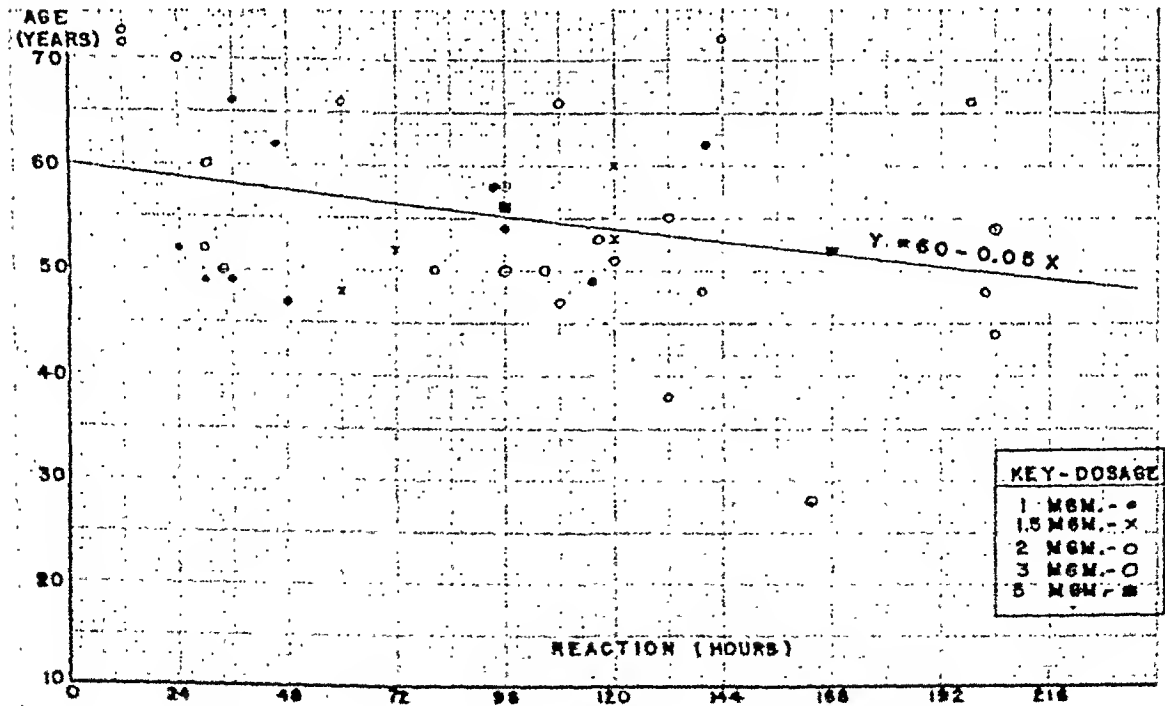


Fig. 4.—The relation of age to the duration of follicular reaction as determined by 3S tests.

It seems logical, therefore, to look upon both the male and the female climacterium as a *glandular imbalance* in which the gonad plays a primary role, rather than a routinely *quantitatively measurable* deficiency in the secretion of a single structure.

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No relationship between particular preparations of the drug, or the menstruum, and the duration of follicular reaction can be demonstrated.

Summary

1. A total of 71 studies in 55 postmenopausal women were made to determine the relative effects of seven different estrogenic preparations.

2. Vaginal smears were obtained prior to injection and at twelve-hour intervals following administration of a *single* dose. Periods of observation ranged from 60 to 377 hours.

3. Three subjects gave no evidence of response. In twenty-four tests, there was an alteration in the type of smear without follicular reaction and in 44 subjects this response was present in varying degree.

4. The degree of follicular reaction and the amount of hormone injected can be directly correlated. An inverse relation exists between age and the height of the follicular reaction.

5. The range of lag-time varied from 42 to 180 hours.

6. An inverse relation exists between lag-time and the amount of hormone injected. The age of the subject is apparently not a factor in the lag-time.

7. The range of duration of follicular reaction varied from twelve to two hundred plus hours.

8. In general, higher dosages tended to produce alterations of longer duration in the vaginal epithelium. Such changes were most marked in subjects of less advanced years.

Conclusions

It is concluded that a single one-milligram dose of either free estradiol or estradiol esters in sesame oil, peanut oil, or propylene glycol is sufficient to stimulate growth and, at least, partial maturation of the vaginal epithelium in most subjects. There appears to be a constant, direct relation between the amount of hormone injected and the length of the lag-time, the degree of follicular reaction and the duration of that reaction.

There is some indication that the esters of estradiol in oily menstrua act more rapidly than either free estradiol, or its esters, in propylene glycol.

There appears to be an inverse relation between age of subject and degree of follicular reaction and, in most instances, between the age of the subject and the duration of the reaction.

Full maturation of the vaginal epithelium of postmenopausal women is dependent, to a great extent, on the amount of hormone injected and on the age of the patient.

The present investigation indicates the importance of the *individual*. Such factors as type of control smear and age are easily determined, but one cannot overlook the fact that patients of the same age will react differently to equivalent doses of estrogen.

These studies place further emphasis on the fact that the doses of estrogen necessary for relief of climacteric symptoms are not quantitatively related to those required to produce a full estrogenic response in the vaginal epithelium.

a distinct advantage in that the exact status of the pelvic viscera could be ascertained. However, this advantage was offset by the difficulty in handling the patients and in interpreting the results. The majority of these patients did not have the ability to evaluate accurately the efficacy of medication so that, at the best, the reports were confusing. Others were too impatient, and, failing to obtain complete relief, tried additional means or, more often, failed to return for follow-up.

The second group of the series was made up of nurses who were suffering from varying degrees of dysmenorrhea. From these patients, the history was most accurate and an excellent record of previous menstrual rhythm was usually available. Examination of the nurses was limited to rectal palpation which is, admittedly, not as conclusive as a routine pelvic. The cooperation of this group was very gratifying inasmuch as they realized the significance of the problem and were most eager to help.

The third group of the series was composed of women employed by a large, local, industrial organization. These patients were never seen personally, but they reported their symptoms of dysmenorrhea to the nurse in charge of the company hospital, who made the diagnosis of essential dysmenorrhea by history, without physical examination of any kind. This approach was not infallible; therefore, many diagnoses were admittedly wrong. It followed logically that some of the failures, which, in honesty, had to be charged against the drug, were, in truth, failures in diagnosis and were caused by definite organic pathology. Interestingly, malingerers soon found a fertile field at the company dispensary. This gradually became a major problem and reached a climax when these patients began appearing at times other than menstruation, realizing that they would not be examined, and need only to report the drug ineffective, to be given time off without loss of pay.

The patients, in all three groups, were given the same glycosidal principle *viburnum prunifolium* in predetermined doses and were given specific instructions regarding how and when to take the medication. This was done with the hope of eliminating as many extrinsic factors as possible. The *viburnum*, prepared according to the method outlined by Krantz and Evans, was packed into capsules and kept in dark, desiccating bottles. Each two-grain capsule of the glycoside, estimated to be the equivalent of 900 grains of the parent *viburnum prunifolium* root bark, was considered as a dose. Each patient was instructed to wait until she had experienced at least thirty minutes of typical dysmenorrhea before taking the first dose of the preparation. This was done to avoid the justifiable criticism offered by those who deny that each cycle results in painful menstruation. The initial dose of two capsules was repeated every two hours until symptomatic relief had been obtained, or a total of ten capsules had been taken. This total dosage, set arbitrarily, was well within the toxic limits, for only an occasional patient complained of mild gastritis which was completely relieved when the medication was discontinued.

Since primary dysmenorrhea is a symptom rather than a specific disease entity, the efficacy of any medication must be judged by the individual. In order to standardize the results as closely as possible, each patient was instructed to evaluate the symptomatic relief according to a specific standard. The dysmenorrhea experienced before the administration of any therapy was considered by the patient as 100 per cent. This was to be used as the basis for estimating the differences in intensity of pain experienced with succeeding cycles. In the subsequent hours of dysmenorrhea, one-half relieved by the medication, the patient would record the residual pain as 50 per cent. It was through these means that we hoped to bring to a definite, uniform, numerical basis the impressions of patients in three very widely separated categories.

THE ROLE OF UTERINE MOTILITY IN ESSENTIAL DYSMENORRHEA

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IN THE past twenty years many excellent papers have appeared in the literature giving detailed classifications of the types of dysmenorrhea, carefully enumerating the more acceptable theories of its etiology, and in many instances, setting forth the results of clinical trials with various therapeutic agents. It is not the authors' intention to review again the problem of painful menstruation, but rather to offer a method which has proved of value in the clinical investigation of essential dysmenorrhea.

During the year 1941, Krantz and Evans, of the Department of Pharmacology at the University of Maryland Medical School, began an evaluation of the pharmacological properties of *viburnum prunifolium*. The discussion of the pharmacological isolation of the active principle of *viburnum* is beyond the scope of this paper and, for this, the reader is referred to the original work on the subject. Suffice it to say that by a tedious and complicated extraction procedure a pure, white crystalline glycoside was obtained. Approximately 100 Gm. of crystals were isolated from 45 kg. of authenticated *viburnum prunifolium* root bark.

The initial evidence from pharmacological studies suggested that the glycoside of *viburnum* was a potent, smooth muscle relaxant. This fact was well established by animal and human uterine muscle experiment, and was reported in 1942 and confirmed by other workers the following year. The drug seemed to have a considerable degree of merit and was even more promising when it was found that the crystals could be packed into capsules, easily stored, and maintained uniform potency over long periods of time. The investigation into its toxic properties showed that, even in extremely large doses, the drug was well tolerated. A mild degree of transitory gastritis was the only untoward effect noted.

Clinical Investigation

It was at this point that the authors were enlisted to carry out the clinical investigation of the therapeutic value of the crystalline glycoside of *viburnum prunifolium*. This work was begun during 1942, using three separate groups of patients, all of whom were of active menstrual age and complained of severe dysmenorrhea. They were selected for the study after a careful history of menstrual rhythm suggested that the dysmenorrhea was essential in character.

The first group, consisting of patients who presented themselves to the Gynecological Dispensary, complaining of dysmenorrhea, was composed chiefly of Negro patients inasmuch as they constitute approximately 75 per cent of the admission to the free clinics at the University of Maryland. This group offered

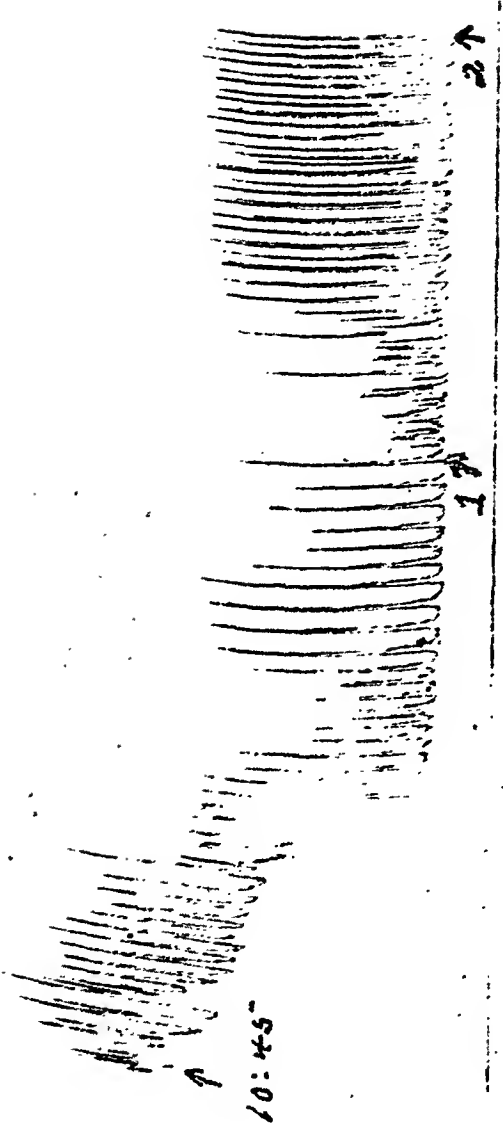


Fig. 1.—Tenth day of cycle. Estrogenic influence apparent. Stabilization 1 hour, 15 minutes. Duration of tracing 3 hours, 30 minutes. Vblurnum, gr. 2, at No. 1, No. 2.

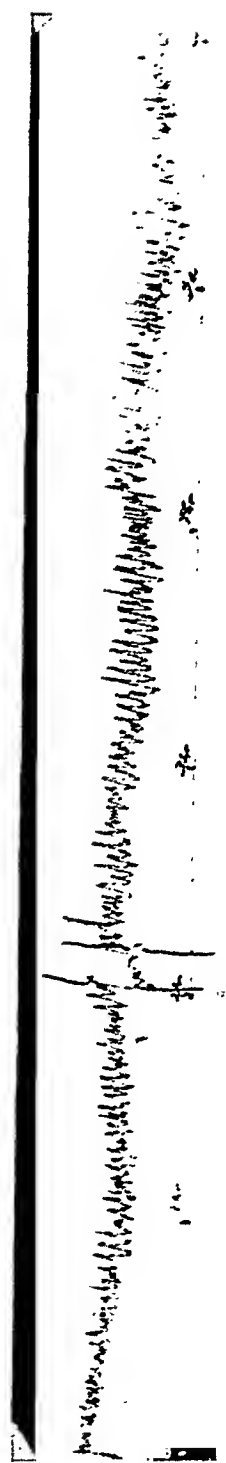


Fig. 2.—Twentieth day of cycle. Moderate progesterogenic influence apparent. Duration of tracing 6 hours.

The records of all three groups were collected and tabulated as to the percentage of relief obtained. In the majority of instances, the results were quite consistent for individual patients; approximately the same degree of benefit was obtained with each bout of dysmenorrhea. Almost any method of therapy and almost any drug will relieve dysmenorrhea, if given to the proper patient at the opportune moment, and when prescribed in adequate amounts. Conversely, there is not a single type of therapy that has cured or relieved all patients. *Viburnum prunifolium* and its glycoside provide to be no exception to this rule and we found that we obtained good relief of pain in only 55 per cent of patients.

Our initial disappointment in this apparently poor therapeutic result led the authors to a careful re-evaluation of our method of study. The successful management of large groups of patients and the accurate interpretation of variations of pain are almost impossible. In addition, we did not feel that this clinical approach gave a true, unbiased, physiologic picture. Moreover, this method failed completely to suggest the mechanism by which *viburnum* brought about the relief of dysmenorrhea.

In laboratory experiments, the glycoside of *viburnum prunifolium* proved itself to be a potent, smooth muscle relaxant. Therefore, we felt any investigation must be carried out on the intact human uterus.

After carefully reviewing the literature and eliminating innumerable approaches and techniques, we elected to study the contractions of the human uterus by means of intra-uterine bag experimentation. Having reached this conclusion, we were then obliged to set up a technique as free of justifiable criticism as possible. Another exhaustive review of the literature convinced the authors that the principles for intra-uterine bag work set forth by Reynolds were best suited.

In all, fifty-three patients took part in this portion of the study of the value of *viburnum*. These patients were all within the child-bearing age and were either entirely normal or had only minor degrees of pelvic pathology. Twenty-nine patients suffered from varying degrees of dysmenorrhea; the remaining twenty-four were completely free of menstrual discomfort. All except three of the group of patients were hospitalized for various reasons. The records taken represent almost every day of the endometrial cycle and during the process of actual menstruation.

Technique

The authors feel that the technique employed has avoided the major pitfalls of intrauterine bag experimentation, and for that reason believe a somewhat detailed description of the method is in order. The table and all other equipment were portable and, therefore, could be easily moved from floor to floor. The patient thus remained in her familiar surroundings. The instruments necessary for pelvic examination, cervical dilatation, and intracavitary exploration were sterilized and packaged. The cannula itself, made of stainless steel, was No. 12 French in size, only slightly greater in diameter than the uterine sound. The distal end of the cannula was covered by a latex balloon which had a maximum capacity of 5.0 c.c. The cannula was sterilized by immersion in Mercurioxy-cyanide solution for a period of one hour.

A tambour diaphragm writing lever made by the Pharmacological Department proved extremely sensitive to even minute changes in pressure. This was a slowly moving smoked paper kymograph completed the equipment.

The patients received no sedation prior to the investigation, so that this would not be a factor in the interpretation of the results. The patients were routinely catheterized and carefully examined. The perineum and vagina were

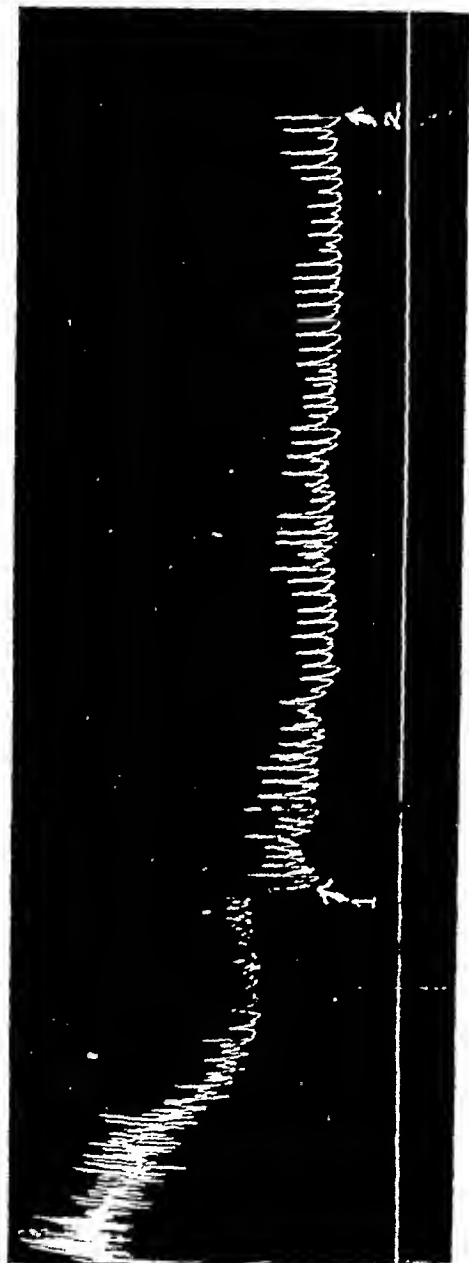


Fig. 3.—Twenty-third day of cycle. Marked progestogenic influence apparent. Stabilization 1 hour, 45 minutes. Duration of tracing 6 hours, 15 minutes. Viburnum, gr. 5, at No. 1.

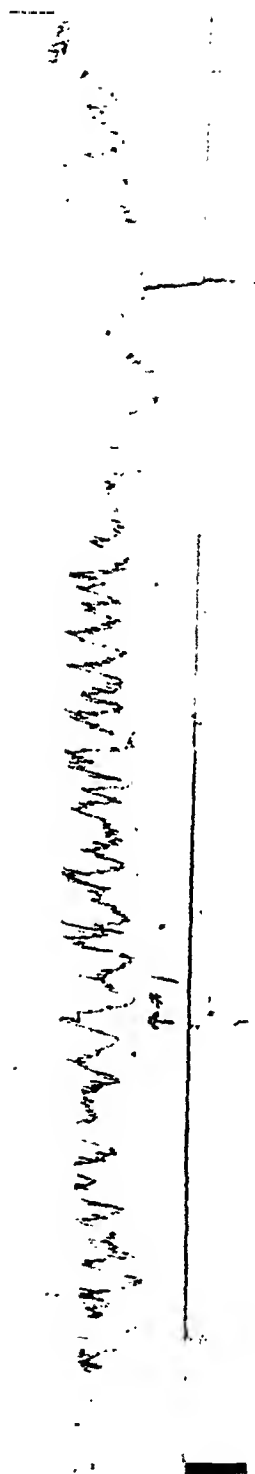


Fig. 4.—Twenty-fifth day of cycle. Maximum progestogenic influence apparent. Duration of tracing 4 hours, 15 minutes. Viburnum, gr. 5, at No. 1.

prepared by a green soap and water technique which has proved most satisfactory in our eystoscopic work.

We were interested to learn that there seemed to be no correlation between the time in the cycle, the intensity of dysmenorrhea experienced, and the degree of cervical dilatation. While this factor was not carefully studied in individual patients, in approximately one-half of the group, the cervix was sufficiently dilated to admit the cannula without preliminary instrumentation. This confirmed the work of Novak who also found it possible to pass freely a sound into the uterine cavity, even at the peak of menstrual pain. These recent experiments tend to refute Mackintosh's classical theory of more than a century ago of "*nulla dysmenorrhea nisi obstructiva*."

The cannula was introduced into the uterine cavity until the fundus was reached. The shaft of the cannula was then fixed to the inner aspect of the thigh by tape, and the vaginal speculum was removed.

The patient was returned to her bed and encouraged to resume the ordinary activity of the ward. She was allowed her regular diet, visitors, and to take part in the usual occupational therapy. However, no medication of any kind was permitted during the day of investigation.

When the patient was thoroughly comfortable, the cannula was connected to the tambour system by means of a length of thick-walled rubber tubing. The pressure within the system was then gradually raised. This was done by the introduction of an antiseptic fluid directly into the lumen of the tubing by means of a sterile syringe and needle. The addition of 3 to 4 c.c. of fluid was sufficient to raise the initial intrauterine pressure to 18 ± 2 mm. as measured on the water-filled manometer.

It was at this point in the experiment that the authors were confronted with the second major pitfall of all intrauterine bag investigation. It is unquestionably true that the introduction of the cannula into the uterine cavity and the increase in intra-cavitary pressure acts as an artificial stimulant to the myometrium. As Reynolds emphasized more than fifteen years ago, time must be allowed for the uterus to adjust to this foreign body, or, as he so well put it, to "unwind."

It is quite obvious that the result of any investigative study undertaken during this period of adjustment would be so altered by gradual decrease of general tonus as to lead to erroneous conclusions. As has been stated previously, the use of air as a medium for intrauterine experimentation is not satisfactory. The gas within the uterine cavity is rapidly influenced by the intra-cavitary temperature and immediately begins to expand. This most certainly raises the pressure within the system, acts as a continuous irritant to the myometrium and prevents the uterus from reaching equilibrium. By our method, namely, with the use of fluid rather than air in the system, and extremely low pressures, we believe we have been able to avoid these very serious criticisms of uterine bag experimentation. We consistently found that the uterus would gradually adjust itself to the foreign body and that, within a period of approximately one hour, equilibrium would be reached and a base line established for that particular tracing. (Figs 1, 3, and 5 show this effect dramatically.) All of our kymographic tracings were made at extremely slow speed; the drum moved at a rate of 25 to 30 mm. per hour. Under these circumstances, the three component factors of uterine physiology, muscle tonus, frequency and the amplitude of contractions could be studied very satisfactorily.

Studies of Uterine Motility

Contrary to common belief, the uterus is constantly active and the examination of the tracings taken before the administration of any medication reveals

very definite patterns which follow an orderly sequence through the several phases of the normal menstrual cycle.

These ever-changing patterns of uterine activity must not be misinterpreted as the response of the organ to medication. Here, again, the authors found exception to the recordings of some investigators who failed to understand the significance of the variations of the tracings. It was, therefore, necessary that tracings be taken during the various portions of the normal cycle to learn to recognize, in the light of the present-day knowledge of uterine physiology, the different patterns that commonly occur and to attempt to understand the process of muscular contractions which bring these about.

During that portion of the cycle influenced by the presence of the estrogenic hormones of the ovary, the so-called "tubal pace maker," described by Hofbauer, Goettler, and, more recently, by Ivy in his work on the primate uterus, is active and finds the myometrium receptive. The rhythmic impulses from the tubal node excite contractions which sweep toward the midline, merge with those initiated at the opposite side and continue downward to terminate in the lower uterine segment. These periodic contractions continue with increasing frequency through the first part of the cycle and reach a peak about the time of ovulation. This activity is translated by the intrauterine recording system as a series of marked, regular contractions of moderate frequency (Fig. 1). The tonus throughout this portion of the cycle is low. By contrast, the tracings taken during the progesterone phase of the endometrial cycle are quite different from those seen under the influence of estrogen. These records suggest that the "tubal pace maker" is no longer receptive. The contractions at this time are no longer rhythmic but apparently originate as isolated muscle groups contract. The frequency of contractions and the amplitude of each wave are diminished. However, the tonus during this phase of the cycle varies but is perceptibly greater than during that portion influenced by estrogenic substance (Figs. 2, 3, and 4). Immediately before the onset of the next menses the former rhythmic contractions reappear and increase quite rapidly in frequency and amplitude as the impending catamenia approaches (Fig. 5). It is extremely interesting to see the parallel between this myometrial activity and the variations in ureteral peristalsis found by the authors in a previous study of the hormonal influences upon the ureter. Apparently the basic principle of response is identical, the variations being a quantitative one, with the uterine muscle receptive to small amounts of estrogenic and progestogenic substances.

The Effect of Viburnum on Uterine Contractions

Having established for ourselves the variations of myometrial activity we were then in a position to study more intelligently the pharmacological action of any particular medication and to evaluate it as a therapeutic agent.

It was neither the intention of the authors to attempt to confirm or refute the findings of other investigators who have studied the problem of dysmenorrhea by means of intrauterine bag experiments, nor was it our purpose to test the therapeutic value of a large group of antispasmodic compounds, but rather as originally planned to devote all our efforts to the complete investigation of the glycoside of viburnum.

However, we had an opportunity to study briefly the pharmacological action of several of the more popular remedies when, for a short time, the supply of patients exceeded the variable supply of the crystalline glycoside. A raspberry leaf tea was tried, primarily because of the reports appearing in English literature. In addition three well-known proprietary preparations, namely Pavatrine,

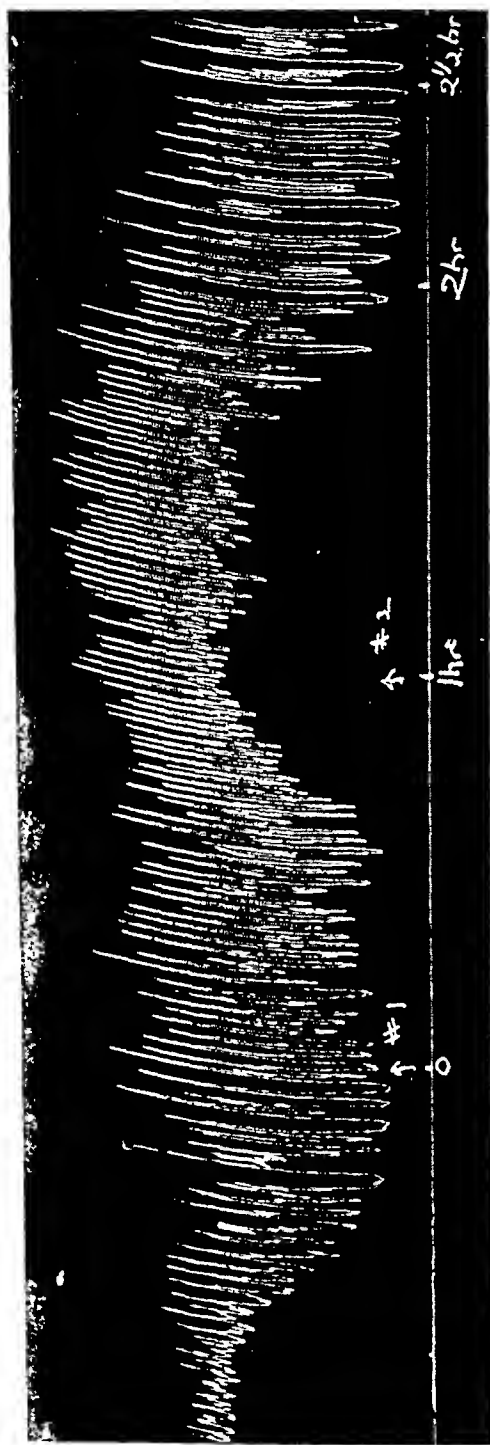


Fig. 5.—Twenty-eighth day of cycle. Resurgence of estrogenic influence apparent. Stabilization 1 hour, 15 minutes. Duration of tracing 4 hours. Viburnum, gr. 5, at No. 1.

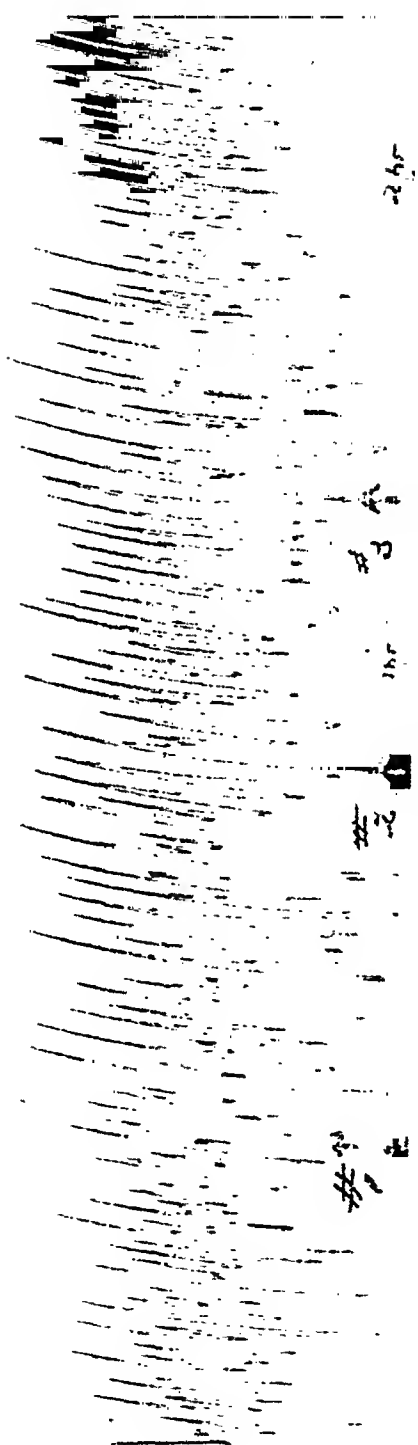


Fig. 6.—Menstruation. Period of stabilization not shown. Duration of tracing 5 hours, 30 minutes. Viburnum, gr. 2, at No. 1, No. 2, No. 3.

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Trasentine, and Depropanex were also used. In each instance the proper technical precautions were observed, sufficient time was allowed for the uterus to reach equilibrium and adequate amounts of tracing were taken. None of the four preparations altered the tonus, decreased the amplitude or interrupted the frequency of the uterine contractions. While we do not feel qualified from this very superficial investigation to express an opinion as to the mode of action of these preparations, it does not appear to be related to the activity of uterine muscle per se.

The glycoside of viburnum was prepared in two forms for the clinical experimentation: an amorphous principle and a dry crystalline powder. The former preparation was deliquescent and proved somewhat unpleasant to taste and its use was soon discontinued so that all effort could be concentrated on the study of the crystalline glycoside. Uterine motility tracings were made by our intraeavitary bag method to study the pharmacological efficacy of the glycoside of viburnum prunifolium. The predetermined dose of the medication, consisting of a 2 grain capsule estimated to be equal to 900 grains of the parent root bark, was given after the ends of the capsule had been pierced to facilitate disintegration more readily. Variations in the tracing during the next thirty minutes were disregarded for it was estimated that at least that length of time was required for absorption of the medication.

Thirty-five tracings were taken to determine the changes, if any, that would be brought about by the action of viburnum on the intact human uterus. The first nine patients were actively menstruating at the time the tracings were made. Four of the patients in this group usually suffered from dysmenorrhea and were experiencing various degrees of discomfort during the process of the actual experiment. In the other five patients, menstruation was a relatively painless procedure which was not appreciably altered by the introduction of the uterine bag. All details of technique as previously described were rigidly followed and adequate amounts of tracing were made, both before and after the administration of the viburnum. A most careful comparison of the tracings revealed no significant difference in any component of contraction between those patients suffering dysmenorrhea, and those in whom the menstruation was painless. While the number studied in this respect is admittedly small (nine) the authors feel that the experiment was controlled carefully enough to make this of significance. It suggests, at least, that the causative factor of dysmenorrhea is possibly not muscular in character.

Eleven patients were in the second week of their menstrual cycle and the records show the effect of estrogens upon the myometrium. Tracings were made on eight patients during the early luteal phase of the cycle. The remaining seven patients were in the last week of the menstrual cycle.

The conclusions arrived at, after a meticulous survey of all thirty-five graphs, were unquestionable and in a sense, not unexpected. Viburnum prunifolium and its crystalline glycoside do not appreciably alter the contractions of the intact human uterus either during the actual process of menstruation, painful or otherwise, or during the portions of the normal menstrual cycle influenced by estrogen or progesterone. (Figs. 1, 3, 4, 5, and 6.)

These findings, while somewhat disappointing, were in keeping with the results of our clinical trials and we could only conclude that the relief obtained was on some basis other than muscular relaxation. It was shortly after the conclusion of this study that Krantz and Evans, continuing their investigation of the pharmacological properties of viburnum, conclusively showed that the glycoside of viburnum was identical chemically with salicin, a glucoside obtained from the bark of the willow or poplar tree.

The answers to these queries are provided by 390 patients who, after having had a vaginal operation, had one or more deliveries at the New York Hospital during the 14-year period from Jan. 1, 1933, to Dec. 31, 1946.

These 390 patients were pregnant 611 times and had a total of 419 operations. These operations were either minor or major. To facilitate classification the following rules were observed:

1. If a minor and a major operation were done simultaneously, only the major operation was considered.
2. If the patient had two operations prior to delivery, the more serious of the two was selected. If the operations were of equal gravity, the one closer to the delivery was selected.
3. Curettage was done as part of all vaginal and cervical repairs.

TABLE I. DISTRIBUTION OF PATIENTS BY YEAR

| YEAR | TOTAL PREGNANCIES | MINOR OPERATIONS | MAJOR OPERATIONS | TOTAL |
|-------|----------------------|---------------------|---------------------|-------|
| 1933 | 3,880 | 9 | 16 | 25 |
| 1934 | 3,785 | 6 | 15 | 21 |
| 1935 | 3,674 | 9 | 17 | 26 |
| 1936 | 3,572 | 14 | 22 | 36 |
| 1937 | 3,636 | 26 | 13 | 39 |
| 1938 | 3,830 | 17 | 16 | 33 |
| 1939 | 3,604 | 17 | 15 | 32 |
| 1940 | 3,626 | 16 | 12 | 28 |
| 1941 | 3,602 | 16 | 8 | 24 |
| 1942 | 3,584 | 8 | 22 | 30 |
| 1943 | 3,517 | 11 | 7 | 18 |
| 1944 | 3,557 | 7 | 5 | 12 |
| 1945 | 3,481 | 12 | 12 | 24 |
| 1946 | 3,943 | 20 | 22 | 42 |
| Total | 51,291 | 188 | 202 | 390 |

Table I shows the incidence of patients by year. Fifteen, or 7.9 per cent, of the patients who had a minor vaginal operation had a simultaneous laparotomy, while 27, or 13.4 per cent, of the patients who had a major vaginal operation, had a laparotomy at the same time. These laparotomies were usually suspensions, occasionally myomectomies, and rarely salpingo-oophorectomy.

Minor Operations

Table II summarizes the data concerning the 188 patients who had minor vaginal operations prior to pregnancy. In not a single case did the previous operation affect pregnancy or labor, nor did labor have any effect on the results of the preceding operations.

Major Operations

The data concerning the 202 patients who had major vaginal operations prior to pregnancy are summarized in Table III.

In this table, anterior repair usually includes plication of the vesical sphincter, posterior repair is equivalent to posterior colporrhaphy and perineorrhaphy, cervical repair means tracheloplasty, while cervical amputation means trachelorrhaphy.

THE OUTCOME OF PREGNANCY FOLLOWING VAGINAL OPERATIONS

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THIS study was undertaken to formulate a plan for the treatment of vaginal lesions during the reproductive years. That such a plan is necessary is evidenced by the wide variance of opinion expressed in the literature.

Leonard,^{1, 2} Rawls,³ and Hunter⁴ are of the opinion that cervical amputation increases the incidence of abortions and premature deliveries and should the pregnancy reach full term "serious dystocia due to cicatricial rigidity of the cervix will commonly be encountered."¹ Novak⁵ states, "There is no unfavorable effect on subsequent labors by the advancement operations. . . . During the reproductive period . . . cervical pathology should be handled as well as possible with more conservative measures such as electrocautery or tracheoplasty." TeLinde⁶ writes: "The vaginal hysterectomy, the transposition operations of Watkins and, to a lesser degree, the Manchester operation are not compatible with future pregnancies." Fothergill⁷ reports that 24 patients who had had previous vaginal operations, including 23 cervical amputations, had 30 pregnancies, 23 of which resulted in spontaneous deliveries, and 7 in operative deliveries. Maier and Thudium⁸ report that in 12 patients with previous vaginal operations, including 10 cervical amputations, there were 10 spontaneous deliveries, three operative deliveries, and one abortion. Shaw⁹ found recurrence in five patients, or 16.5 per cent, of 30 who had pregnancies after vaginal repairs. He noted no difficulty during labor and was of the opinion that labor was shortened owing to the removal of part of the cervix. Gordon¹⁰ writes: "Some gynecologists remain unconvinced that women can be safely carried through parturition without severe dystocia or serious damage to the plastic end result. Yet many who have performed this operation upon young women have reported no serious dystocia or any pathology in the puerperium." This is a bare sample of the divergent opinions which are prevalent in the literature. Leonard,^{1, 2} and Gordon¹⁰ provide excellent surveys of the literature.

Object

This analysis aims to determine:

1. At what age, parity, degree, and duration of symptoms vaginal operations have been performed during the childbearing period.
2. Whether future childbearing may be permitted, if such an operation has been done.
3. Whether, if childbearing is permitted, such delivery may be vaginal or must be by cesarean section.
4. If the delivery has been by the vaginal route, what effect the repair has on labor and conversely how labor affects the repair.

TABLE III. MAJOR OPERATIONS

| NAME OF OPERATION | NUM- BER | PER CENT | DURATION OF SYMP- TOMS PRIOR TO OPERA- TION (YEARS) | AGE AT OPERA- TION | PARITY AT OPERA- TION | TIME LAPSE SINCE OPERA- TION (YEARS) | AGE AT PREG- NANCY | PREGNANCIES | | | | | | | | TOTAL | | |
|--|-------------|-------------|---|-----------------------------|--------------------------------|---|-----------------------------|--------------------------|----------------|-----------------------|----------------|-----------------------|----------------|-----------------------|----------------|-------|--|-----|
| | | | | | | | | ABORTION AND IMMATURE | | PREMATURE | | FULL TERM | | | | | | |
| | | | | | | | | SPON- TANE- OUS | OPERA- TIVE | SPON- TANE- OUS | OPERA- TIVE | SPON- TANE- OUS | OPERA- TIVE | SPON- TANE- OUS | OPERA- TIVE | | | |
| | | | | | | | | | | | | | | | | | | |
| I. <i>Vagina</i> | | | | | | | | | | | | | | | | | | |
| 1. Anterior repair | 2 | 1.0 | ? | 33.0 | 1.0 | 3.5 | 36.5 | | | | | | 2 | | | | | 2 |
| 2. Posterior repair | 19 | 19.5 | 2.5 | 29.1 | 2.0 | 3.4 | 32.5 | 1 | 4 | | | | 21 | | | | | 28 |
| 3. Repair third degree laceration | 10 | 3.0 | 0.7 | 24.8 | 1.3 | 5.2 | 36.0 | | 1 | | | | 7 | | | | | 15 |
| 4. Anterior and posterior repair | 31 | 15.5 | 3.6 | 31.5 | 3.0 | 3.5 | 35.0 | 1 | 4 | | 1 | | 24 | | | | | 36 |
| 5. Reconstruction of vagina | 1 | 0.5 | ? | 22.0 | 0 | 11.0 | 33.0 | | | | | | | | | | | 2 |
| 6. Repair vesico-vaginal fistula | 4 | 2.0 | 0.5 | 25.0 | 1.0 | 5.2 | 30.2 | | 2 | | | | 3 | | | | | 7 |
| 7. Repair recto-vaginal fistula | 14 | 6.5 | 2.6 | 26.7 | 1.0 | 4.3 | 31.0 | 6 | 2 | | | | 16 | | | | | 29 |
| II. <i>Cervix</i> | | | | | | | | | | | | | | | | | | |
| 8. Cervical repair | 24 | 12.0 | 2.6 | 26.0 | 1.3 | 5.0 | 31.0 | 13 | 3 | 5 | 1 | | 41 | | | | | 70 |
| 9. Cervical amputation | 22 | 11.0 | 0.3 | 30.0 | 2.0 | 4.0 | 34.0 | 1 | 3 | 2 | 2 | | 10 | | | | | 25 |
| III. <i>Cervix and Vagina</i> | | | | | | | | | | | | | | | | | | |
| 10. Anterior repair, cervical repair | 1 | 0.5 | 1.0 | 30.0 | 2.0 | 12.0 | 4.2 | | | | | | 1 | | | | | 1 |
| 11. Anterior repair, cervical amputation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | | | | | 0 |
| 12. Posterior repair, cervical repair | 6 | 3.0 | 2.3 | 32.0 | 2.0 | 4.5 | 36.5 | 1 | 2 | | | | 4 | | | | | 10 |
| 13. Posterior repair, cervical amputation | 6 | 3.0 | 4.0 | 31.0 | 2.2 | 3.3 | 34.3 | | 2 | | | | 6 | | | | | 9 |
| 14. Anterior and posterior repair, cervical repair | 9 | 4.5 | 3.5 | 33.7 | 2.5 | 2.9 | 36.6 | | 3 | | | | 5 | | | | | 10 |
| 15. Anterior and posterior repair, cervical amputation | 31 | 15.0 | 2.7 | 34.0 | 3.0 | 3.2 | 37.2 | 3 | 6 | 1 | | | 16 | | | | | 45 |
| 16. Interposition operation | 1 | 0.5 | ? | 32.0 | 2.0 | 4.5 | 36.5 | | 1 | | | | | | | | | 2 |
| 17. Unspecified vaginal and/or cervical operation | 21 | 10.5 | 3.0 | 22.2 | 2.9 | 8.4 | 30.6 | 6 | 3 | 2 | | | 23 | | | | | 40 |
| Total | 202 | 100.0 | 2.6 | 29.0 | 1.6 | 5.3 | 34.3 | 32 | 36 | 10 | 4 | | 179 | | | | | 331 |

TABLE II. MINOR OPERATIONS

| NAME OF OPERATION | NUM- BER | PER CENT | DURATION OF SYMP- TOMS PRIOR TO OPERA- TION (YEARS) | AGE AT OPERA- TION | PARITY AT OPERA- TION | TIME LAPSE SINCE OPERA- TION (YEARS) | AGE AT PREG- NANCY | PREGNANCIES | | | | | | TOTAL | | |
|--|-------------|-------------|---|-----------------------------|--------------------------------|---|-----------------------------|--------------------------|----------------|-----------------------|----------------|-----------------------|----------------|-------|--|--|
| | | | | | | | | ABORTION AND IMMATURE | | OPERATIVE | | FULL TERM | | | | |
| | | | | | | | | SPON- TANE- OUS | OPERA- TIVE | SPON- TANE- OUS | OPERA- TIVE | SPON- TANE- OUS | OPERA- TIVE | | | |
| I. <i>Perineum and Vagina</i> | | | | | | | | | | | | | | | | |
| 1. Fistula-in-ano excision | 5 | 2.7 | 0.4 | 29.5 | 1.0 | 3.0 | 32.5 | | | | | 6 | 1 | 7 | | |
| 2. Excision rectal prolapse | 1 | 0.5 | ? | 21.0 | 0 | 4.0 | 25.0 | | | | | | 1 | 1 | | |
| 3. Excision hypertrophic labia | 1 | 0.5 | ? | 26.0 | 0 | 0.9 | 27.0 | | | | | | 1 | 1 | | |
| 4. Excision labial cyst | 2 | 1.0 | ? | 24.5 | 0 | 5.0 | 29.5 | | | | | 5 | | 5 | | |
| 5. Fulguration condyloma acuminata | 2 | 1.0 | 0.3 | 23.5 | 0 | 2.0 | 25.5 | | | | | 1 | 2 | 3 | | |
| 6. Excision Bartholin's cyst or abscess | 21 | 11.4 | 2.4 | 27.0 | 0.5 | 3.0 | 30.0 | 2 | 1 | 1 | | 21 | 6 | 31 | | |
| 7. Urethral operations | 2 | 1.0 | 0.3 | 27.5 | 2.5 | 1.5 | 29.0 | | 2 | 1 | | | 1 | 4 | | |
| II. <i>Vagina</i> | | | | | | | | | | | | | | | | |
| 8. Hymenectomy | 12 | 6.5 | 2.5 | 26.0 | 0.1 | 3.5 | 29.5 | 1 | 2 | | | 10 | 9 | 22 | | |
| 9. Dilatation of vagina | 6 | 3.2 | 5.0 | 28.4 | 0 | 4.2 | 32.6 | | 1 | | | 9 | 1 | 11 | | |
| 10. Excision vaginal cyst | 4 | 2.1 | ? | 25.2 | 0.75 | 3.1 | 28.3 | 1 | | | | 2 | 1 | 4 | | |
| 11. Drainage vaginal abscess | 4 | 2.1 | ? | 20.5 | 0.5 | 6.3 | 26.8 | 2 | | | | 4 | 1 | 7 | | |
| 12. Excision vaginal septum | 2 | 1.0 | ? | 23.5 | 0 | 17.8 | 40.3 | | 1 | | | 6 | 1 | 8 | | |
| 13. Vaginal polypectomy | 3 | 1.6 | 1.6 | 28.0 | 0.3 | 3.5 | 31.6 | 1 | | | | 1 | | 2 | | |
| 14. Posterior colpotomy | 3 | 1.6 | 0.1 | 26.3 | 1.0 | 5.6 | 32.0 | | 2 | | | 1 | | 3 | | |
| III. <i>Cervix</i> | | | | | | | | | | | | | | | | |
| 15. Cauterization | 41 | 21.8 | 1.0 | 28.0 | 1.25 | 3.8 | 31.8 | 1 | 6 | | | 36 | 15 | 58 | | |
| 16. Cauterization and curettage | 34 | 18.2 | 1.0 | 25.9 | 1.0 | 9.5 | 35.4 | 5 | 4 | 1 | | 29 | 10 | 49 | | |
| 17. Dilatation and/or curettage | 14 | 7.5 | 6.0 | 28.2 | 0.1 | 4.4 | 32.6 | 1 | 4 | | | 6 | 7 | 18 | | |
| 18. Myomectomy | 1 | 0.5 | 1.0 | 33.0 | ? | 5.0 | 38.0 | | 1 | | | 1 | 1 | 3 | | |
| 19. Polypectomy | 23 | 12.2 | 0.3 | 30.7 | 6.5 | 7.1 | 37.8 | | 4 | | | 20 | 8 | 32 | | |
| 20. Polypectomy and curettage | 5 | 2.1 | 1.3 | 32.0 | 0.2 | 2.8 | 34.8 | | 1 | | | 6 | 2 | 9 | | |
| 21. Stem pessary | 2 | 1.0 | 8.5 | 30.0 | 0 | 2.5 | 32.5 | | 1 | | | 1 | | 2 | | |
| Total | 188 | 100.0 | 2.3 | 30.0 | 0.5 | 4.6 | 31.7 | 14 | 30 | 3 | | 165 | 68 | 280 | | |

The various effects of vaginal operation on pregnancy and labor are outlined in Table IV. Two therapeutic abortions were performed because of recent extensive repairs. In view of the relatively small number of complications and the possibility of obviating vaginal delivery by cesarean section, these appear unwarranted. The incidence of abortion and premature labor was not higher than the clinic average. The cervix dilated without undue difficulty and cervical lacerations were not more extensive or more frequent than was customary. The descent of the head was frequently delayed by the vaginal scars. Deep midline episiotomies were occasionally necessary to facilitate descent. The most striking effect was the increase in cesarean section. Seventeen, or 8.5 per cent, of these patients were delivered by cesarean section. This is more than twice the clinic incidence of 3.8 per cent in 1946.

TABLE V. EFFECT OF LABOR ON VAGINAL OPERATION

| OPERATION | EFFECT ON REPAIR | | | | | | NO EFFECT ON REPAIR | | TOTAL |
|---|------------------|-----------------------------------|---------------------------------|--------------------------|-------------|-------------|---------------------|-------------|-------|
| | RECUR- RENCE | VAGI- NAL RE- LAXA- TION | VAGI- NAL LACER- ATION | SECOND OPERA- TION | NUM- BER | PER CENT | NUM- BER | PER CENT | |
| I. <i>Vagina</i> | | | | | | | | | |
| 1. Anterior repair | 1 | | | | 1 | 50 | 1 | 50 | 2 |
| 2. Posterior repair | 4 | | | | 4 | 22 | 15 | 78 | 19 |
| 3. Repair third degree laceration | | 1 | | 1 | 2 | 20 | 8 | 80 | 10 |
| 4. Anterior and posterior repair | 6 | | | 2 | 8 | 16 | 23 | 74 | 31 |
| 5. Reconstruction of vagina | | | | | 0 | 0 | 1 | 100 | 1 |
| 6. Repair of vesico-vaginal fistula | | | | | 0 | 0 | 4 | 100 | 4 |
| 7. Repair of recto-vaginal fistula | 2 | | | | 2 | 17 | 12 | 83 | 14 |
| II. <i>Cervix</i> | | | | | | | | | |
| 8. Cervical repair | 5 | | | | 5 | 21 | 19 | 79 | 24 |
| 9. Cervical amputation | 2 | | | | 2 | 9 | 20 | 91 | 22 |
| III. <i>Cervix and Vagina</i> | | | | | | | | | |
| 10. Anterior repair, cervical repair | | | | | 0 | 0 | 1 | 100 | 1 |
| 11. Anterior repair, cervical amputation | | | | | 0 | 0 | 0 | 0 | 0 |
| 12. Posterior repair, cervical repair | 1 | | | | 0 | 17 | 5 | 83 | 6 |
| 13. Posterior repair, cervical amputation | | | 2 | | 2 | 33 | 4 | 67 | 6 |
| 14. Anterior and posterior repair, cervical repair | | | | 1 | 1 | 11 | 8 | 89 | 9 |
| 15. Anterior and posterior repair, cervical amputation | 4 | | | 2 | 6 | 21 | 25 | 79 | 31 |
| 16. Interposition operation | | | | | 0 | 0 | 1 | 100 | 1 |
| 17. Unspecified vaginal and/or cervical operation | 7 | | | | 7 | 33 | 14 | 67 | 21 |
| Total | 32 | 1 | 2 | 6 | 41 | | 161 | | 202 |
| Percentage | 16 | 0.5 | 1 | 3 | 20.5 | | 79.5 | | 100 |

Pregnancy and labor caused recurrence in 32 patients (16 per cent) and necessitated a second operation in six patients (3 per cent). The influence of labor upon the preceding vaginal operation is illustrated in Table V.

Certain of these operations deserve more than tabular analysis. There were only two recurrences in the 15 patients who were allowed to deliver vaginally following repair of vaginal fistulas. This observation is at variance with the

TABLE IV. EFFECT OF OPERATION ON PREGNANCY AND LABOR

| OPERATION | EFFECT ON LABOR | | | | | | | | | | NO EFFECT ON LABOR | | TOTAL |
|--|----------------------|------------------|----------------------------|-----------------------------|---------------------|--------------------------|--------------|-------------------|-------|----------|--------------------|----------|-------|
| | THERAPEUTIC ABORTION | PRE-MATURE LABOR | POOR CERVI-CAL DILA-TATION | DELAYED DESCENT DUE TO SCAR | CERVICAL LACERATION | DEEP MID-LINE EPIS-OTOMY | LOW FOR-CEPS | CESA-REAN SECTION | TOTAL | PER CENT | NUM-BER | PER CENT | |
| | | | | | | | | | | | | | |
| I. <i>Vagina</i> | | | | | | | | | | | | | |
| 1. Anterior repair | | | | | | | | | 0 | 0 | 2 | 100 | 2 |
| 2. Posterior repair | | | | | | | | | 0 | 0 | 19 | 100 | 19 |
| 3. Repair third degree laceration | | | | | | | | 1 | 4 | 40 | 6 | 60 | 10 |
| 4. Anterior and posterior repair | | | | 1 | 1 | 1 | 1 | 2 | 5 | 16 | 26 | 84 | 31 |
| 5. Reconstruction of vagina | | | | | | | | 1 | 1 | 100 | 0 | 0 | 1 |
| 6. Repair of vesico-vaginal fistula | | | | | | | | 1 | 1 | 25 | 3 | 75 | 4 |
| 7. Repair of recto-vaginal fistula | | | | 1 | | 1 | | 2 | 4 | 30 | 10 | 70 | 14 |
| II. <i>Cervix</i> | | | | | | | | | | | | | |
| 8. Cervical repair | 1 | 1 | 1 | | | | | 1 | 4 | 17 | 20 | 83 | 24 |
| 9. Cervical amputation | | | | | | | | 2 | 2 | 9 | 20 | 91 | 22 |
| III. <i>Cervix and Vagina</i> | | | | | | | | | | | | | |
| 10. Anterior repair, cervical repair | | | | | | | | | 0 | 0 | 1 | 100 | 1 |
| 11. Anterior repair, cervical amputation | | | | | | | | | 0 | 0 | 0 | 0 | 0 |
| 12. Posterior repair, cervical repair | | | | | | | | | 0 | 0 | 6 | 100 | 6 |
| 13. Posterior repair, cervical amputation | | | | | | | | 1 | 1 | 17 | 5 | 83 | 6 |
| 14. Anterior and posterior repair, cervical repair | 1 | | | 2 | | | | 2 | 5 | 56 | 4 | 44 | 9 |
| 15. Anterior and posterior repair, cervical amputation | | | | | | | | | 6 | 21 | 25 | 79 | 31 |
| 16. Interposition operation | | | | | | 1 | 1 | 1 | 1 | 100 | 0 | 0 | 1 |
| 17. Unspecified vaginal and/or cervical operation | | | | | | 1 | | 1 | 2 | 8 | 19 | 92 | 21 |
| Total | 2 | 1 | 1 | 7 | 1 | 4 | 3 | 17 | 36 | | 166 | | 202 |
| Percentage | 1 | 0.5 | 0.5 | 3.5 | 0.5 | 2 | 1.5 | 8.5 | 17.6 | | 82.4 | | 100 |

TABLE VII. MULTIPLE OPERATIONS

| NAME OF OPERATION | TWO OR MORE BEFORE DELIVERY | | ONE BEFORE DELIVERY AND ONE AFTER | | TWO BEFORE DELIVERY AND TWO AFTER | | TOTAL | |
|--|-----------------------------|-----------|-----------------------------------|-----------|-----------------------------------|-----------|----------|-----------|
| | PATIENTS | OPERATION | PATIENTS | OPERATION | PATIENTS | OPERATION | PATIENTS | OPERATION |
| Third degree laceration | 1 | 4 | 2 | 4 | 1 | 3 | 2 | 4 |
| Anterior and posterior repair | 1 | 3 | 3 | 6 | | | 5 | 13 |
| Reconstruction of vagina | 2 | 8 | | | 2 | 6 | 1 | 3 |
| Rectovaginal fistula | 1 | 2 | | | | | 4 | 14 |
| Anterior and cervical repair | | | | | | | 1 | 2 |
| Anterior, posterior and cervical repair | | | 1 | 2 | | | 1 | 2 |
| Anterior and posterior repair, cervical amputation | | | 2 | 4 | 1 | 3 | 3 | 7 |
| Unspecified | | | 1 | 2 | | | 1 | 2 |
| Total | 5 | 17 | 9 | 18 | 1 | 3 | 18 | 47 |

TABLE VIII. EFFECT OF MAJOR VAGINAL OPERATIONS ON LABOR

| | NUM- BER | PER CENT | NUM- BER | PER CENT |
|-----------------------------|-------------|-------------|-------------|-------------|
| 1. Effect on labor | 17 | 8.5 | 36 | 17.6 |
| Cesarean section | 7 | 3.5 | | |
| Delayed descent due to scar | 4 | 2.0 | | |
| Deep midline episiotomy | 3 | 1.5 | | |
| Low forceps | 2 | 1.0 | | |
| Therapeutic abortion | 1 | 0.5 | | |
| Premature labor | 1 | 0.5 | | |
| Poor cervical dilatation | 1 | 0.5 | | |
| Cervical laceration | 1 | 0.5 | 166 | 82.4 |
| 2. No effect on labor | | | 202 | 100.0 |
| Total | | | | |

TABLE IX. EFFECT OF LABOR ON MAJOR VAGINAL OPERATIONS

| | NUMBER | PER CENT | NUMBER | PER CENT |
|---------------------------|--------|----------|--------|----------|
| 1. Effect on operation | | | 41 | 20.5 |
| Recurrence | 32 | 16.0 | | |
| Second operation | 6 | 3.0 | | |
| Vaginal laceration | 2 | 1.0 | | |
| Vaginal relaxation | 1 | 0.5 | 161 | 79.5 |
| 2. No effect on operation | | | 202 | 100.0 |
| Total | | | | |

experience of Thomas¹¹ who reports, "The descent of the head in vaginal deliveries is bound to stretch the scar of a healed fistula, and, considering the difficulties involved in so unfortunate an occurrence, classical cesarean section seems justifiable in all cases which one sees before labor begins and considerations of sepsis do not prohibit." Only one of the nine patients who delivered vaginally after repair of a third degree laceration suffered from recurrence.

Faulty cervical dilatation occurred only once. The preceding operation had been a cervical repair. In the only case in which repeated premature labor occurred, the preceding operation also had been a cervical repair. This disagrees with Leonard,² who concluded that tracheloplasty had no effect on labor, while trachelorrhaphy had marked effects.

The so-called Manchester operation had comparatively minor effects on the course of labor, but recurrence occurred in four cases and two secondary operations were necessary. The one case in which pregnancy occurred after an interposition operation required cesarean section because of a posterior sacculation of the uterus.

Discussion

Our analyses have given a retrospective view of the operation from the vantage point of delivery. An equally informative viewpoint would have been from the time of operation forward to the time of delivery.

Few obstetrical operations are included, although it is obvious that some such operations, such as Dührssen's incisions, are far more extensive than many of the gynecologic operations.

The contrast between the minor and major operations is striking. As shown in Table VI the patients who had minor operations are younger, have had fewer children prior to operation and, lastly, their operations had no adverse effects on labor. The patients who had major vaginal operations were older, had more children, their operations adversely affected their labors at times and their labors not infrequently had a harmful effect on the vaginal repairs.

TABLE VI. CONTRAST BETWEEN MAJOR AND MINOR OPERATIONS

| | MINOR | MAJOR | TOTAL |
|---------------------------------|-------|-------|-------|
| Total patients | 188 | 202 | 390 |
| Duration of symptoms (years) | 2.3 | 2.6 | |
| Age at operation | 27.1 | 29.0 | |
| Parity at operation | 0.5 | 1.6 | |
| Age at pregnancy | 31.7 | 34.3 | |
| Total pregnancies | 280 | 331 | 611 |
| Effect on labor | 0 | 36 | |
| Percentage | 0 | 17.6% | |
| Effect on repair | 0 | 42 | |
| Percentage | 0 | 20.5% | |
| Total operations | 188 | 231 | 419 |

Table VII illustrates that 18 (9 per cent) of these patients required more than one operation. A total of 47 operations was performed. Only 13 of these had to be performed after pregnancy while 34 were necessary prior to pregnancy. Some patients had as many as three to five operations prior to pregnancy.

SOLID TERATOMA OF THE OVARY, WITH REPORT OF FIVE CASES

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DERMOID cysts of the ovary, although by far the most common, represent only one type of ovarian teratoma. Blackwell and his co-workers find that they comprise 5 per cent of all ovarian neoplasms at the Mayo Clinic. Other investigators find their incidence even higher, and Geist quotes figures which vary from 10 to 34 per cent of all ovarian tumors. At the Johns Hopkins Hospital the figure is about 5 per cent of all neoplasms of the ovary and about 10 per cent of all cystic tumors. There have been 100 cases among the last 15,000 case specimens in the Laboratory of Gynecological Pathology. This represents a five-year span, or an average of about twenty cases a year.

Much less common than its benign counterpart is the solid teratoma or teratoblastoma. Geist collected eight in 1,100 ovarian neoplasms of all types, including 184 cystic teratomas. This incidence is somewhat higher than that found by others. Kernauner reported two solid teratomas among 283 dermoids, and Mayer, one of 131. Only two such cases have been found in the last twenty years among more than 35,000 patients treated in the Department of Gynecology at the Johns Hopkins Hospital during that period. Several other such specimens have been sent in for diagnosis from outside clinics, and these are not included. Excluded also are the few cases in which there is considerable difference of opinion and doubt as to the interpretation of the tumor.

One serious difficulty is at once apparent to anyone who looks over the literature on these types of tumors; namely, the criteria of differentiation between the so-called cystic dermoids and the solid teratomas. Novak gives three general points of distinction, although he agrees that there is considerable divergence of opinion and some overlapping of the groups.

1. The dermoid is a cystic tumor, and the teratoma primarily a solid one, although it may contain cystic areas.

2. The dermoid is predominantly ectodermal, although mesoderm and entoderm are often found. The teratoma usually shows elements from all three germinal layers.

3. The dermoid cyst is a benign tumor with well-differentiated tissue elements. The teratoma is a malignant tumor, containing highly differentiated and often bizarre conglomerations of fetal elements.

It has been mentioned that solid teratoma may present cystic areas; conversely, dermoids may contain more solid areas. Moreover, in the study of one hundred dermoid cysts by Blackwell and associates, it was found that 100 per cent of the tumors contained ectodermal tissue, 93 per cent mesodermal, and 71 per cent entodermal. His feeling is that further sections might well have revealed close to 100 per cent of both mesodermal and entodermal elements.

Summary

An attempt has been made, by studying 390 patients who had deliveries after vaginal operations, to formulate a plan for the treatment of vaginal lesions in women during the childbearing age. One hundred eighty-eight of these operations were minor, while 202 were major. The minor operations had no effect on labor, nor did labor have any effect on the operative results. The major operations had two main effects on labor.

As shown in Table VIII these were:

1. Delayed descent of the head because of scar in seven (3.5 per cent) patients.

2. Delivery by cesarean section in 17 (8.5 per cent) patients. This is two and one-half times the clinic incidence. Table IX shows that labor affected the operative results after major vaginal operations in two ways:

1. Recurrence occurred in 32 (16 per cent).

2. Secondary operations were necessary in six (3 per cent).

The majority of patients with rectovaginal fistulas, vesicovaginal fistulas, third degree lacerations, amputations of the cervix, alone or with anterior and posterior vaginal repair, delivered vaginally without too many untoward results. A pregnancy following the interposition operation in the series, resulted in cesarean section because of a posterior sacculation of the uterus. The patients who had major vaginal operations were older and had had more children than those who had minor vaginal operations.

Formulation

When symptoms or signs warrant, minor and major vaginal operations may be performed on women of the childbearing age. It is not necessary to urge that childbearing be completed prior to the operation. Such operations should be compatible with future childbearing. In certain instances they may be performed with the understanding that, should recurrence follow further childbearing, a secondary operation will be necessary. Should pregnancy occur after vaginal operation, there is no indication to interrupt the pregnancy. The majority of such patients deliver vaginally. Occasionally a deep midline episiotomy is necessary to facilitate the descent of the head which has been impeded by vaginal scarring. In certain instances, such as severe symptoms, extensive repairs, or multiple operations before the attainment of a satisfactory result, the danger of injury to the vaginal tissue should be obviated by cesarean section.

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It occurs disproportionately often in young individuals, is much less inclined to be bilateral than are dermoids, and although often encapsulated tends strongly to perforate the capsule and spread both by extension and metastasis. Radiotherapy seems to help very little, although the treatment of choice is still radical surgery and deep x-ray.

Five cases of teratoma are reported here. Two of these are from the Gynecological Service of the Johns Hopkins Hospital and are the only two such cases encountered in the past twenty years. Two of them are from the Harriet Lane Home for Invalid Children at the Johns Hopkins Hospital and are also the only two true teratomas in the last two decades. The fifth and last is a private case.

Case Reports

CASE 1.—A colored female, aged 31, para vi, was admitted to the hospital on Feb. 28, 1928, complaining of lower abdominal pain of six weeks' duration. The past history was completely negative. The patient stated that for some six weeks she had noticed an increasing discomfort in the lower abdomen and had been aware more recently of the presence of a mass. She had had anorexia for about two months, with a weight loss of approximately twenty pounds in the preceding three months.

On admission, the hemoglobin was only 55 per cent; white count, 12,000; temperature, 101° F. X-ray films of the abdomen showed the diaphragm raised and lungs compressed by the presence of fluid in the abdomen. No masses were visualized.

The abdomen was full and tense, and a fluid wave could be elicited. A mass could be felt arising from the pelvis. It was nodular and fixed. The pelvic examination showed normal external genitals, outlet and a clean, smooth cervix. None of the pelvic organs were felt as such, being obscured by a large nodular mass that arose from the left adnexal area.

On March 6, 1928, an exploratory laparotomy was performed. Approximately 3,500 c.c. of serosanguineous material was drained off. The omentum was found to be studded with necrotic hemorrhagic nodules. A large 20 cm. mass, rough, nodular and necrotic, was found in the right pelvis, seemingly arising from the left ovary on a pedicle. The right ovary was enlarged and firm, and the liver was enlarged and nodular. In view of the "hopeless situation" the operator simply ligated the pedicle and removed the tumor mass. The patient withstood the procedure well but went into shock after being returned to the wards, dying the same afternoon despite appropriate therapy. Autopsy revealed extensive metastases in the peritoneum, omentum, right ovary, and liver, but not in other regions.

The specimen was, grossly, a large soft tumor 18 cm. in diameter and seemed to be partially encapsulated. It was soft, hemorrhagic, and necrotic, and there was no tendency to papillary formation.

Microscopically (Fig. 1) the tumor showed a dense fibrous stroma infiltrated by sheets of large, clear, oval cells with large oval nuclei in a generally bizarre invasive pattern. There was considerable variation in size and staining quality. Several areas of cartilage could be found and in other areas (Fig. 2) there were glandlike spaces lined by epithelium varying from a low cuboidal to a high columnar. The metastatic areas showed only disorderly patches of large oval cells infiltrating the tissues.

CASE 2.—A colored woman, aged 57, para ii, was admitted to the hospital on Sept. 20, 1946, complaining of pain in the lower abdomen. The past history showed only a syphilitic infection which had been treated throughout 1945. Menopause had occurred eight years before after an uneventful menstrual era. There had been no postmenopausal bleeding until the present illness. For about a month there had been a gradually increasing discomfort and pain in the lower abdomen and back. Three days prior to admission slight vaginal spotting was noted which persisted up to the present time. No other symptoms were noted.

This would seem to dispel one of the time-honored criteria for differentiation, so that now all we can say is that dermoids generally contain a preponderance of ectodermal structures.

Of more value is the histologic pattern. Teratomas generally show a conglomerate collection of tissue, in all degrees of differentiation, generally embryonal. As a rule, there is little evidence of orderly organ formation. Simple cystic dermoids may show just about any type of tissue or organ (except gonadal), and Geist has painstakingly listed them. As a rule, these are highly differentiated, with little suggestion of the bizarre, disorderly tissues characterizing the typical teratoma. After all, therefore, the fundamental difference between the simple dermoid and the teratoma, in the sense in which this latter term is ordinarily applied, is that the alien tissues of the dermoid are of mature well-differentiated type, while those of the teratoma include many cells of immature type, with the same capacity for unrestrained growth which characterizes malignant growths in general.

In even the benign dermoid one element may predominate and seem to blot out the others. Both pseudomucinous and Brenner tumors have been shown to arise in this fashion. Struma ovarii, in which functionally active thyroid tissue may thus be dominant, is another illustration of this growth. Still another interesting lesion is the primary chorionepithelioma of the ovary, which may, at times, arise from a teratoma wherein the trophoblastic elements have blotted out all of the other tissues. There have been a small number of these in which the possibility of a previous ovarian or tubal pregnancy has been excluded, as in young girls or virgins. For some unknown reason, they are far less common than chorionepithelioma of the male testis.

The complex histology of the teratomatous group of tumors creates an obvious difficulty to precise classification, for the means that we have available for this are limited. It has been shown that either the benign dermoid or the malignant teratoma may contain all three cell layers and that either may be partially solid or cystic. There remains only the microscopic pattern to determine how the tumor shall be classified, supplemented by the criteria for tumors in general. If the neoplasm presents a disorderly, highly undifferentiated growth of bizarre-looking cells, it is obviously malignant. For lesser degrees of such change, there will still remain unfortunately a divergence of interpretation among various observers. It is in cases of this borderline type, as in borderline and doubtful ovarian tumors in general, that the Ovarian Tumor Registry may ultimately serve a valuable purpose.

I would like to propose that the word teratoma be confined exclusively to the solid type of tumor and be considered malignant by definition. The benign cystic variety should be referred to simply as dermoids (and not cystic teratomas). If there is some type of malignant degeneration of the dermoid, the designation of malignant dermoid might be used. Admittedly this is not a perfect plan of classification, for there are always intermediate types of borderline malignancy, but there are similar degrees between an adenoma malignum and a solid type of adenocarcinoma. For the present, however, if the word teratoma be reserved for the solid malignant type of lesion, we have at least achieved a start toward a more orderly type of classification.

Teratoma, then, is a highly malignant neoplasm, probably 50 to 75 per cent of these tumors terminating fatally, according to the best available figures.

On admission the temperature was normal; hemoglobin, 12.5 Gm.; the white count, 6,600. Abdominal palpation revealed an irregular nontender mass in the left lower quadrant, arising from the pelvis. On pelvic examination, just below and to the left of the urethra, there was seen an indurated, friable ulcer 1 cm. in diameter. The cervix was small and atrophic. The whole pelvis was filled with an irregular nodular fixed mass which seemed to arise from the left adnexal area. No organs were palpable.

On September 23 dilatation and curettage, with biopsy of the cervix and vulvar ulcer, were done. The pathologic report of the section of the ulcer showed "undifferentiated adenocarcinoma, probably metastatic to the vulva." Other reports were irrelevant.

On September 27 an exploratory laparotomy was done. A vascular, nodular, but fairly well-encapsulated mass was found displacing the fundus posteriorly. Neither ovary nor tube could be identified separately and seemed to be part of the mass. The liver felt normal, and there were no implants in the peritoneum or omentum. A necrotic grayish-red area could be seen at the rectosigmoidal junction and seemed to be about the size of a walnut. A subtotal abdominal hysterectomy with bilateral salpingo-oophorectomy was done. Biopsy of the nodule of the rectosigmoidal junction was not performed because the patient went into very profound shock and was taken off the table in a precarious condition. She responded well, however, to blood, plasma, and fluids and had an essentially uneventful postoperative course, being discharged from the hospital on the twelfth postoperative day. At the time of discharge pelvic examination revealed bilateral induration in the broad ligament areas but no discrete masses.

The gross specimen was reported as follows: There was a large tumor mass, measuring 11 by 9 by 7 centimeters. It was solid, nonecystic, and partially encapsulated. The tissue was very friable and necrotic, and there were numerous hemorrhagic areas. Neither ovary nor the right tube could be identified. The left tube lay across the tumor mass and seemed to be thickened and indurated.

Microscopic sections of the tumor mass showed a disorderly growth of primary undifferentiated adenocarcinoma with only slight attempts at gland formation. There was infiltration everywhere in solid sheets. There were numerous areas of young cartilage cells, which varied widely in size and staining quality. No bone was seen. There was extensive vascularization, and numerous areas of necrosis and scarring were visible (Fig. 3).

The uterus contained a few myomatous nodules and showed a chronic endometritis. No ovarian tissue could be found. In the one tube that could be identified there were metastatic nodules of rather solid adenocarcinomatous type (Fig. 4).

The patient returned for examination on Oct. 28, 1946, at which time she was found to have nodules in the left broad ligament. Deep x-ray therapy was begun, and twenty treatments were given, one every other day. Ten thousand roentgens were given, through two anterior and two posterior pelvic portals (15 by 15), using the 400 kv. machine.

After completion of x-ray therapy the patient was seen again on January 27; at this time she was found to have an enlarged nontender mass in the right upper quadrant, presumably the liver, and extensive nodular induration throughout the whole pelvis. She died at home on March 6, 1947, and no autopsy was performed.

CASE 3.—A colored child, 4 years of age, was apparently quite well until May, 1946, when she began to vomit, feel weak, and complain of pain in the lower abdomen. At this time her mother noticed an abdominal mass and took her to the Children's Hospital in Washington, D. C.

Exploratory laparotomy was done on June 20. A degenerating solid tumor 11 cm. in diameter was found arising from the right ovary and extending into the leaves of the broad ligament and the mesentery of the small bowel. As much of the tumor as possible was removed, but complete removal was technically impossible.

Postoperatively the child did well for about a month, at which time nausea and vomiting, anorexia, and drowsiness began. Swelling of the abdomen became visible. The child was admitted to the Harriet Lane Home for Children at the Johns Hopkins Hospital in

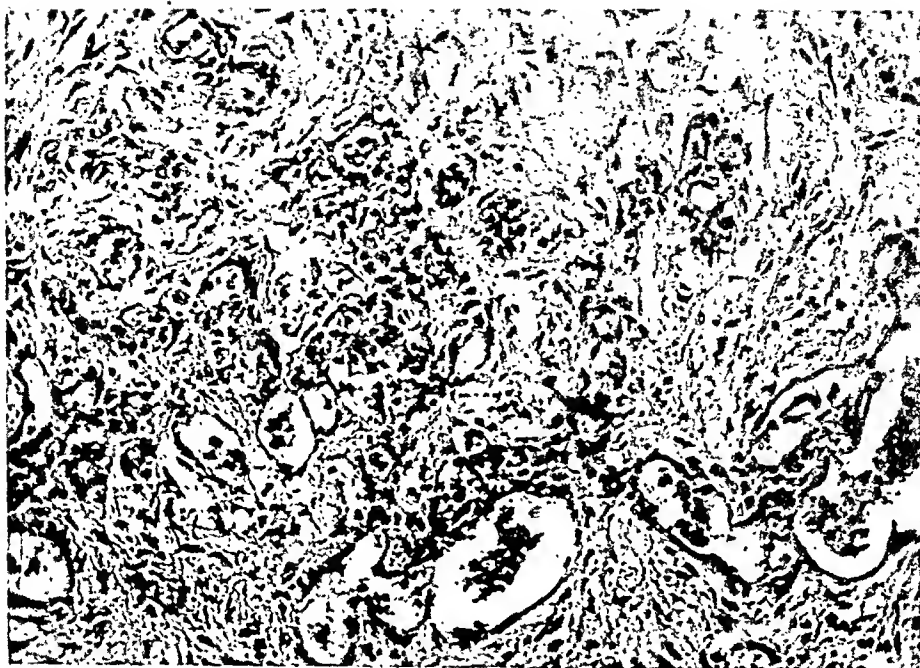


Fig. 1.—Case 1. Representative area.

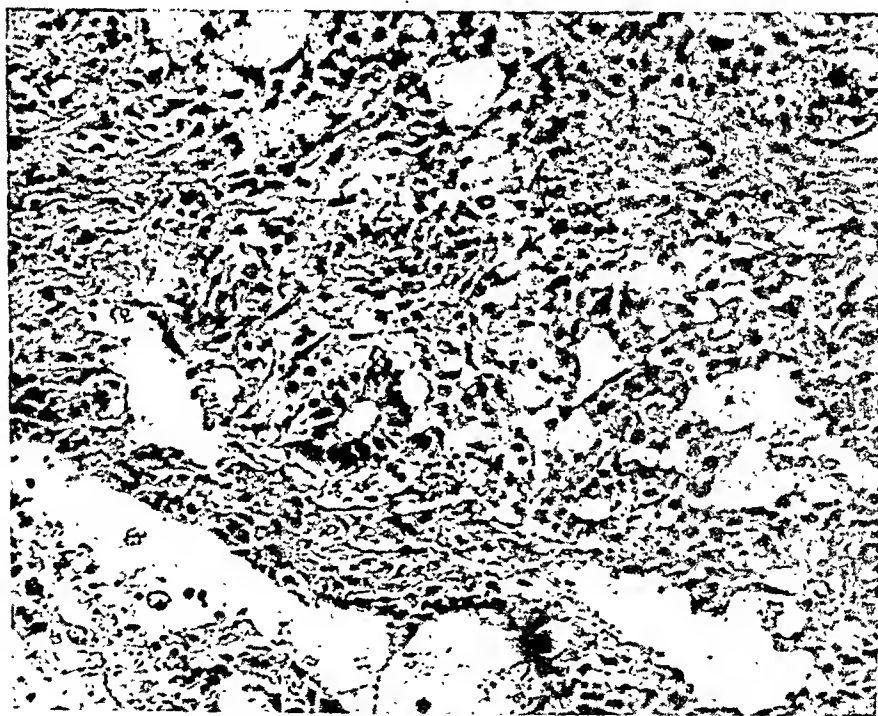


Fig. 2.—Case 1. In about the middle of the field a glandlike area lined by a tall epithelium with basal nuclei can be seen. Surrounding this are invasive areas of malignant cells (with many areas of degeneration and necrosis).

August, 1946. At the time the hemoglobin was 50 per cent; white count, 17,000; temperature, 101° F. Examination showed an abdomen grossly distended by the presence of a large mass that filled the pelvis and arose 6 cm. above the iliac crest, more on the right than the left. X-ray films confirmed the presence of this mass that filled the pelvis and arose 6 cm. above the iliac crest, more on the right than the left. No metastases were seen in the chest or the long bones.

Pathologic reports and sections were obtained from the Children's Hospital in Washington. Microscopic sections of the tumor showed a mixed type of growth. There were all types of gland acini with crude duct formation lined with epithelium varying from a flat to a high columnar type. The stroma was dense, in places appearing myxomatous and in others sarcomatous. Mitoses were present but in small numbers, although there was marked variation in cellular detail and a highly infiltrative pattern (Fig. 5).

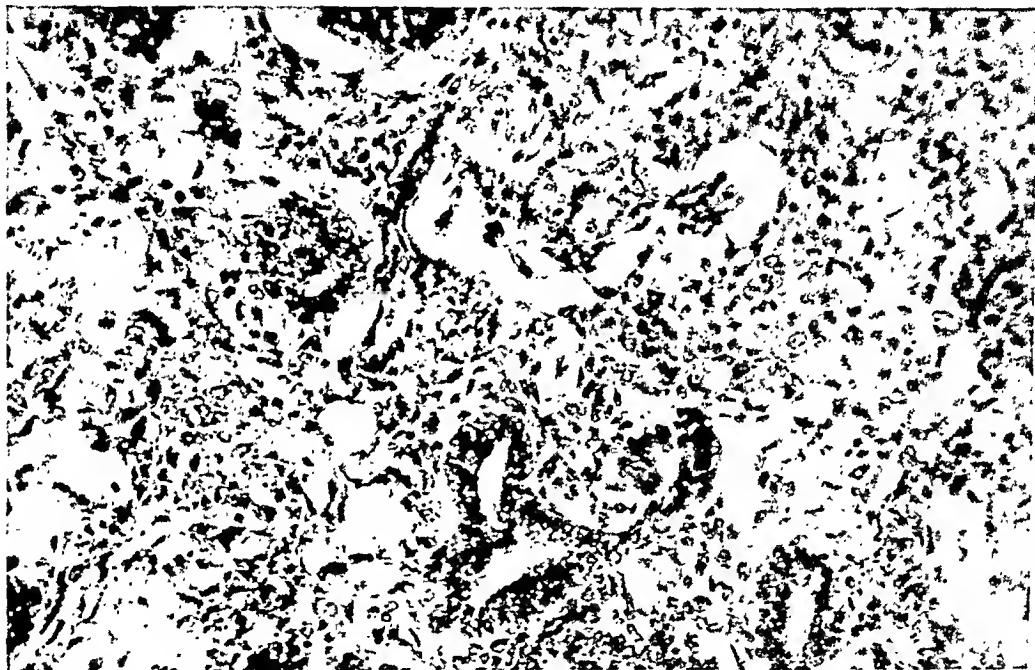


Fig. 5.—Case 3. Unidentifiable gland structures in fibrosarcomatous matrix.

The patient was started on deep x-ray therapy, receiving biweekly treatments of 100 r. through two anterior (15 by 15) portals with the 200 kv. machine. The patient tolerated this type of therapy poorly, being nauseated constantly. During this treatment the abdominal mass was actually observed to enlarge, and x-ray therapy was therefore discontinued after a total of only 600 r. was given. The case was considered hopeless, but at the parents' request the patient was allowed to go home, where she died shortly thereafter.

CASE 4.—A white child, aged 12 years, was admitted to the Harriet Lane Home for Invalid Children on Aug. 30, 1933. The past history was not remarkable. About a year prior to admission she had begun to have intermittent attacks of pain in the lower abdomen, generally after eating. These attacks became progressively more frequent and severe, and shortly before admission an abdominal mass was noticed by the family.

On admission the temperature was normal; hemoglobin, 83 per cent; white count, 8,100 with a normal differential. Abdominal palpation revealed a mobile, firm mass larger than a grapefruit, which seemed to arise from the pelvis. The mass contained alternate hard and cystic areas. X-ray films revealed a tumor mass in the lower abdomen and pelvis, with calcified areas. Gastrointestinal series and chest plates were negative.

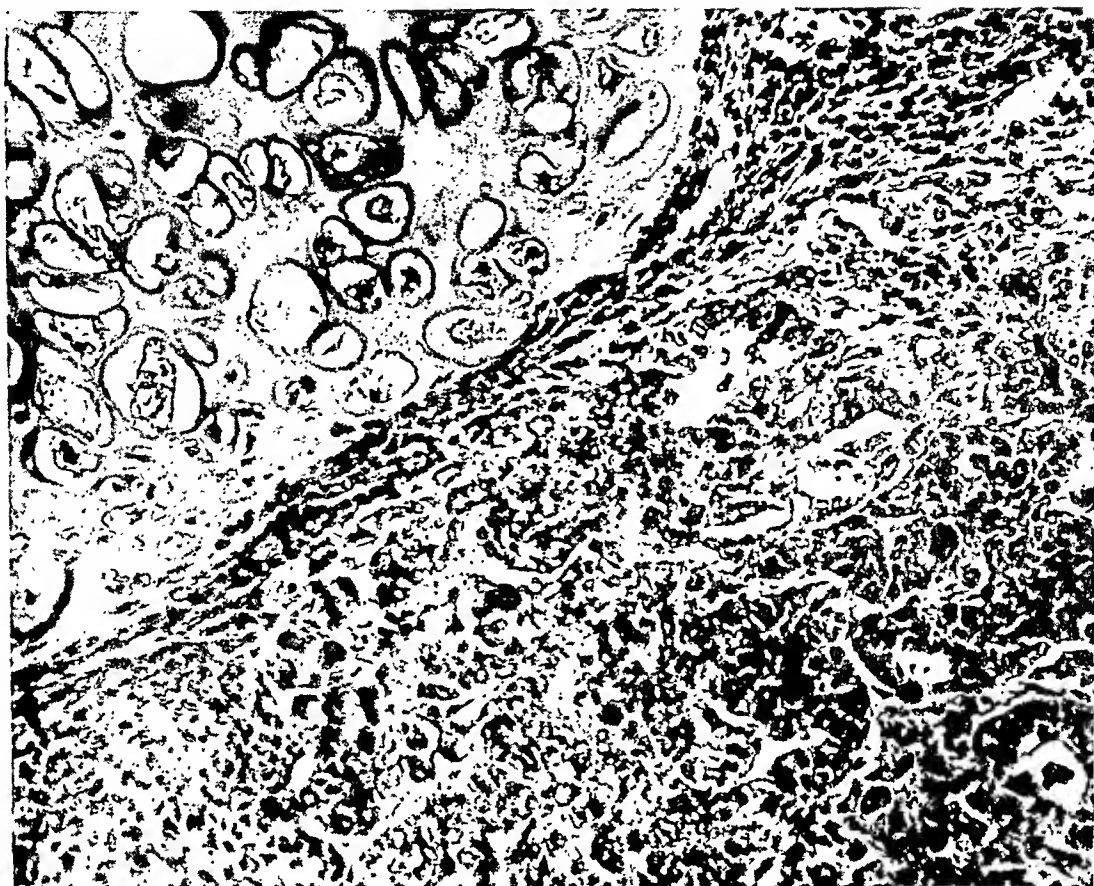


Fig. 3.—Case 2. At the top immature cartilage is readily discernible. At the bottom are several glandlike structures surrounded by sheets of rather solid adenocarcinoma.



Fig. 4.—Case 2.—At the top the wall of the tube can be seen. Extending into it from below is the same adenocarcinomatous growth seen in Fig. 3.

Examination at this time revealed a bulging, tense abdomen with definite ascites. The tumor was one fingerbreadth above the umbilicus and hard and nodular. At least one irregular, firm mass could be felt in the pelvis. There was marked pitting edema of both legs. X-ray films showed soft tissue masses in the lower abdomen but no evidence of bone or chest metastases. Both diaphragms were elevated, which suggested intra-abdominal fluid.

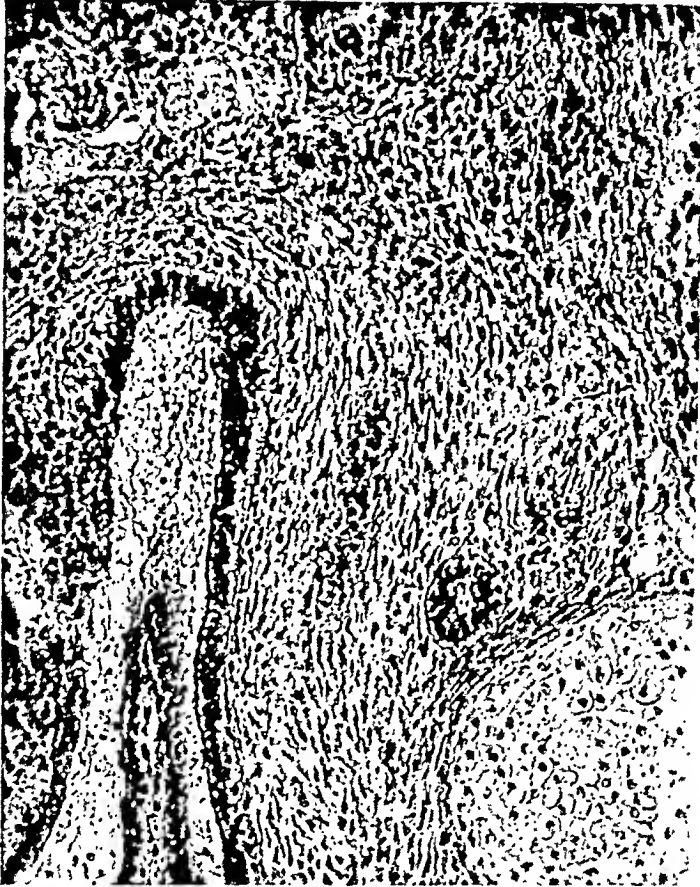


Fig. 7.—Case 5. Rather mature looking cartilage and well-differentiated ducts are seen. The stroma is likewise orderly and highly differentiated.

X-ray therapy was not thought worth while, and routine palliative paracenteses and analgesia were carried out. The patient deteriorated rapidly and died on March 11, 1934.

Autopsy was performed and showed recurrence of the tumor in the region of the left ovary with metastases to liver, lung, peritoneum, omentum, and bronchial, tracheal, and retroperitoneal lymph nodes.

CASE 5.—A white woman, 33 years of age, para iii, was admitted to St. Joseph's Hospital, on Feb. 15, 1944 (private patient of Dr. Thomas K. Galvin). The past history was non-contributory. The patient stated that for three months she had had lower abdominal pains aggravated by the menses. During this time the periods which had previously lasted five days were prolonged to eight days and had been more profuse.

On examination abdominal palpation revealed a mobile, nontender mass filling the pelvis up to the level of the umbilicus. Pelvic examination showed the mass to be partially cystic and arising from the left adnexal area.

A total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed the following day. Grossly the right ovary was represented by a mass measuring 18 by 10 by

On Sept. 14, 1933, exploratory laparotomy was performed. A smooth, vascular mass, about 15 by 20 cm. was found arising from a pedicle which seemed to be attached to the left broad ligament. The mass was grayish-white, irregular, but not papillary. The tumor was removed by simple ligation of the pedicle, and the patient was returned to the wards in good condition.

Gross pathologic report showed that the tumor weighed 2,000 grams and measured 22 by 18 by 10 centimeters. The surface was smooth and glistening, and the mass felt generally fluctuant, although several very hard, cartilaginous structures could be palpated. On section many small cystic areas were found, from which a yellow, cheesy matter could be expressed. Hair, cartilage, and bone seemed to line some of these cavities. In others there was a firm, papillary type of tissue.

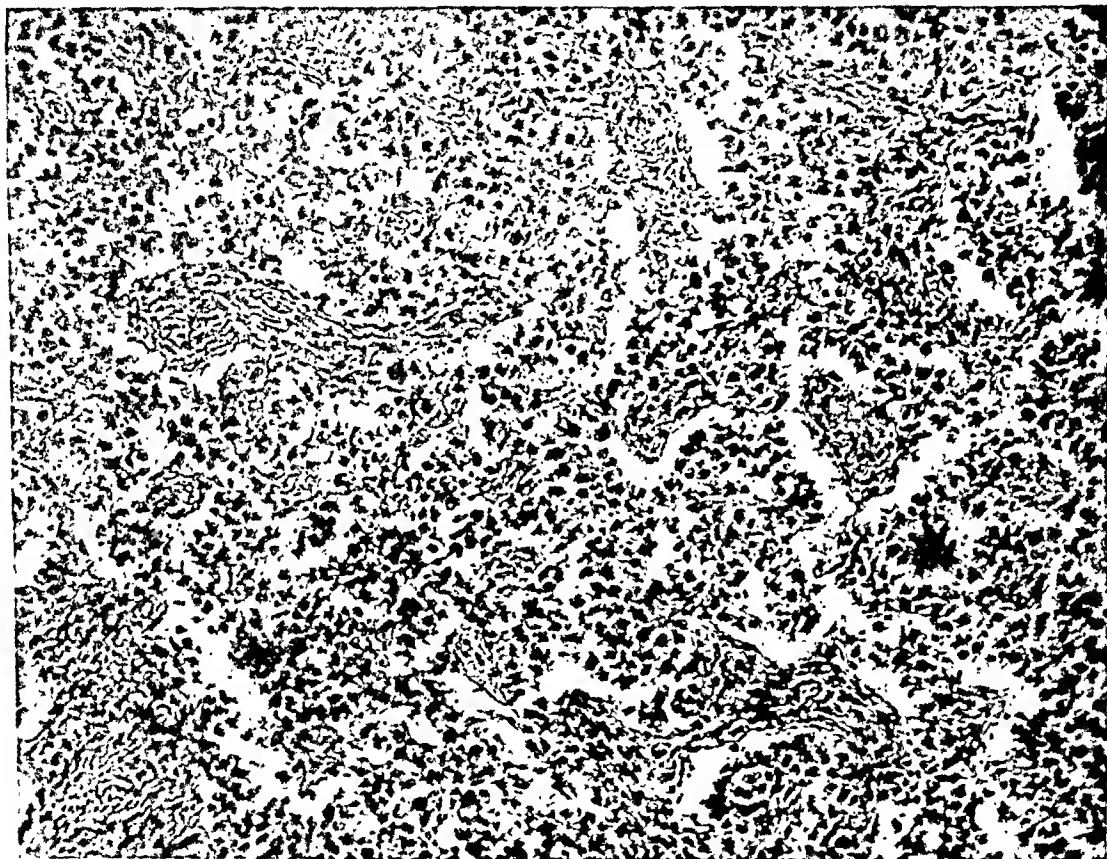


Fig. 6.—Case 4. Area resembling alveolar carcinoma.

Microscopically, derivatives of ectoderm, mesoderm, and entoderm could be found. Sections showed cartilage, bone, hair follicles, intestine, and sebaceous glands. Present in many areas was an invasive type of epithelial growth composed of large oval cells, arranged in septa (Fig. 6). The nuclei were small and showed considerable hyperchromatosis. The cells showed marked variation in size and staining quality, and a markedly invasive pattern was present. Many mitoses could be found.

The patient's postoperative course was a model one, and she was discharged Sept. 24, 1933, to be followed in the Outpatient Department. She was seen on several occasions, and no evidence of recurrence was found. Meanwhile, the child was attending school and felt well. Around the first of February, 1934, she began to complain of abdominal pain and was brought to the Dispensary on February 13.

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9 centimeters. The surface was lobulated and smooth but contained many cystic areas. On sectioning the mass a cloudy amber fluid escaped, and a solid area could be seen, measuring 10 cm. in diameter. This was grayish-white in appearance and had a whorl-like appearance. The uterus, left ovary, and both tubes appeared normal.

Microscopically, sections from the ovarian mass showed a mixture of all types of tissues, representing the three germinal layers. There were numerous ducts and glands lined with epithelium varying from a low cuboidal to a high columnar. There were many cystic areas lined with a typical pseudomucinous type of epithelium. Numerous hair follicles, sweat glands, areas of bone and cartilage formation, nervous tissue, fat, and connective tissue could be found. There were areas showing many innoeous-appearing squamous cell nests. Blood supply was abundant. There were numerous areas showing elements bearing a strong resemblance to both alimentary and respiratory mucosa. Everywhere the cells appeared to be highly differentiated, and there was no suggestion of an infiltrative pattern (Fig. 7). The uterus, both tubes, and left ovary were microscopically normal.

The patient's postoperative course was smooth and uncomplicated. She had had repeated re-examinations, and as late as July 26, 1947, she was asymptomatic and without evidence of a recurrence.

Comment

The first four of the cases reported here are classic examples of the highly malignant teratoma. The duration of symptoms was short, and yet the tumor was far advanced. The age incidence in the first two cases is somewhat higher than that generally quoted, but the average for the four is only 26 years. It is likewise of interest to note that two of the four patients who died received deep x-ray therapy, but nevertheless the tumor spread rapidly. This is too small a series, however, to conclude that x-ray therapy is worthless. In all of the four cases ending fatally the histologic pattern was that of a highly undifferentiated, disorderly malignant type of tumor, which picture was paralleled by the clinical course.

An interesting sideline to the last case is the varied classification applied to the tumor by the five experts of the Ovarian Tumor Registry to whom the tumor was later submitted. Two members called the tumor simply teratoma, one called it a teratoma, benign, another designated it as teratoma (embryonal), and the last considered it to be a dermoid cyst. From this it seems apparent that the word teratoma has a diverse connotation to different individuals and illustrates the confusion on this point, even among trained pathologists.

In any event, the histologic pattern in his last case is vastly different from that seen in the other four. All three germinal layers are represented, but there is no disorderly bizarre pattern of infiltration. The cells are highly differentiated, and there is a fair, though imperfect, attempt at actual organ formation. The whole picture is that of a lesion that is either benign or of a very low grade of malignancy. This is likewise borne out by the patient's course, for she is alive and well three years after operation.

It should be apparent that there is no justification from a prognostic or statistical standpoint in placing tumors of this nature in the same category with the previous four. While it is true that the histologic pattern is our only valid criterion and that there will always be individual differences of interpretation, better standardization of terms would help to clarify a difficult enough problem. Some type of classification such as that suggested earlier in this paper seems practicable and should lessen the confusion which exists as to the proper application of the designation of ovarian teratoma.

One of our cases, Mrs. M. E. M., was completely studied for the presence of estrone and progesterone in the tumor tissue and the findings are reported herein. A pregnanediol excretion analysis run on a twenty-four-hour urine specimen was also negative. This unopposed activity by the biologically active substance has been well pointed out by Traut and Butterworth,¹ who feel, on the one hand, that, although these tumors do not excrete excessively large amounts of estrogenic substance, the secondary hormonal effects are in all probability produced by its long continued and constant action, and, on the other hand, that there is no opposed corpus luteum effect in most cases. We have determined this active substance in equivalents of estrone and have shown, at least in one case, that there was no progesterone, in spite of the fact that grossly the tumor presented a bright yellow color and gave a "lenteinized" appearance.

Material

It is the purpose of this paper to present 15 cases of theca-cell tumor of the ovary from the Wisconsin General Hospital of the University of Wisconsin and the State Laboratory of Hygiene of the State of Wisconsin. The latter is a general laboratory service provided for the people of Wisconsin, to render laboratory service through the physicians and hospitals of the state, and is located as a part of the University. Many of these tumors have been confused with fibromas of the ovary because of the similarity in both the gross and microscopic appearance. It is necessary, therefore, that any review must include a careful study of all previous cases diagnosed as fibroma of the ovary. This was done in each case covering the five-year period of 1941 to 1946 in the State Laboratory of Hygiene and the fifteen-year period of the University Hospital, ending in 1946. From this study there were 12 cases from the former and 3 from the latter, making a total of 15 cases which are presented in this paper. Dockerty,² in 1940, reported 10 cases and Banner and Dockerty¹⁴ added 13 new cases in 1945. These reports represent the largest single collection of tumors up to this time.

Symptomatology and Clinical Characteristics

These tumors usually occur in postmenopausal women and the average age in the 15 cases reported here is 54 years, with 31 years as the youngest and 73 years as the oldest. The average age of the 70-odd cases collected from the literature is 52 years, the youngest being 16 years and the oldest 92 years, as reported by Patterson⁶ in 1936. This 92-year-old patient had postmenopausal bleeding and enlargement of the uterus with endometrial hyperplasia. It is interesting to note that there has not been a case reported in the literature as occurring prior to the age of puberty. This is in sharp contrast to the granulosa-cell tumor which has been frequently reported as occurring in the first decade of life (5 to 10 per cent) and which is also an estrogen producer. Of the 15 cases presented here, 61.5 per cent of the patients were 50 years of age or older. Banner and Dockerty,¹⁴ in summarizing their combined 23 cases, found their average age to be 53.5 years with 65 per cent in excess of 50 years of age. At least 80 per cent of their patients had borne children.

It has been estimated by von Szathmary¹ that theca cell tumors make up 4.4 per cent of solid ovarian tumors. Banner and Dockerty¹⁴ found that their series comprised 3 per cent of solid ovarian tumors and that theca-cell tumor was less than one-tenth as common as ovarian fibroma. It is with the latter that this tumor is most often confused, and, if accurate pathologic examination could be obtained on all such tumors, the incidence would undoubtedly be greater. McGoldrick and Lapp,¹⁵ in reviewing their material, found 3 thecomas, 4 granulosa-cell tumors, 2 dysgerminomas and 1 luteoma in 176 ovarian tumors at large, or a 1.7 per cent incidence for thecoma.

THECA-CELL TUMORS OF THE OVARY WITH A REPORT OF FIFTEEN CASES AND A REVIEW OF THE LITERATURE

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THE specialized tumors of the ovary have given cause for much interest and investigation, not only because of their neoplastic properties but because of the biologic activity of certain members of this group. The granulosa-cell tumor was the first of this group, described by von Kahliden,¹ in 1895, and classified by Robert Meyer in 1915. However, it was not until 1932, that the last member of this interesting group of tumors was reported by Loeffler and Priesel² to which they gave the name "fibroma theca cellulare xanthomatodes ovarii," more commonly known as the theca-cell tumor of the ovary.

Since this original report, much interest has developed over these tumors and writers throughout the world have made numerous reports of the clinical and pathologic findings. Today there are seventy-odd cases reported in the English and American literature alone, and a tumor which was once thought to be rare is much more frequent in occurrence than this would indicate. As will be noted when their histology is discussed, they are difficult of recognition, particularly to the inexperienced gynecologic pathologist. Melnick and Kanter³ recorded the first two cases in the American literature in 1934, and since that time frequent reports have followed.

Thecoma has gradually become recognized as a pathologic entity and is now being separated from fibroma of the ovary with which it was previously confused. Certain theca-cell tumors present areas containing granulosa cells which made Novak and Gray⁷ propose a common origin. They found classification into distinct groups difficult at times and did not propose too strict a classification. Another factor which may substantiate this belief is that of those tumors analyzed for biologic activity only estrogenic substance has been found.^{9, 12} Unfortunately, the diagnosis is seldom suspected preoperatively, which prevents proper evaluation and preparation for endocrinologic studies. The pathologist most often makes the diagnosis and by that time the tissue has been fixed in formalin, which renders it unfit for biologic assay. In the survey of the literature made here, it is noted that there are only three reports of a biologic analysis made on tissue of a theca-cell neoplasm. One of these was the report of Geist,⁹ in 1935, which was expressed in mouse units. Geist and Spielman,¹³ in 1935, using an extract of tumor tissue, substantiated the presence of estrogenic substance which was suspected clinically by Melnick and Kanter.³ Banner and Doekerty's¹⁴ tumor showed no estrogen. These facts help to explain the many reports of postmenopausal bleeding, associated endometrial hyperplasia, and the occasional occurrence of endometrial cancer. Moreover, the action of this estrogenic substance seems to be unopposed, as there has never been reported associated corpora lutea, progesterone, or the presence of pregnanediol in the urine of these patients.

plasia, adenomyosis, hypertrophy of the myometrium with uterine enlargement, uterine myomas and transitory hyperplasia of the gland fields of the breast. The occasional association of thecoma with endometrial carcinoma has also been discussed on this basis. The bleeding often assumes a cyclic character and may be associated with enlargement of an atrophic uterus and a recrudescence of the sex desire. Breast, long atrophic, may show transitory hyperplasia of the gland fields. In the premenopausal woman, menstrual irregularities are not the rule, as they may be masked by the normal cyclic function.

Most of the cases reported here and collected from the literature presented tumors large enough for either abdominal or pelvic palpation and were most frequently diagnosed preoperatively as myomata of the uterus. However, they may be of any size, as one tumor,⁵ found incidentally on section of a surgical specimen, measured only 2 mm. in diameter.

There has never been reported a case of bilateral thecoma. McGoldrick and Lapp¹⁵ and Patterson and McCullagh⁶ both reported cases with a fibroma of the opposite ovary. The latter report concerned a 92-year-old woman with a thecoma in one ovary and a fibroma of one inch in diameter in the other ovary. Banner and Dockerty¹⁶ found that the right ovary was the seat of the tumor in 15 cases and the left ovary in 8 cases. Torsion of the tumor on its pedicle has been reported six times.^{7, 15} Free peritoneal fluid is not uncommonly encountered at operation in the amounts usually seen with any large nonmalignant tumor, being reported as present in 8 cases.¹⁵ Mendel and Tyrone¹⁷ reported a case of thecoma of the ovary and hydrothorax (Meigs syndrome) in a 44-year-old woman who developed ascites and right hydrothorax associated with a 12 by 7 by 7 cm. tumor, which was also associated with a myomatous uterus.

Endometrial hyperplasia was found in 19 of 50 cases (38 per cent) collected from the literature.¹⁻¹¹ McGoldrick and Lapp¹⁵ collected 46 cases with endometrial findings and 36 of these showed hyperplastic changes, of which 32 were in the postmenopausal group. It is difficult to estimate the frequency with which endometrial hyperplasia occurs, because of the few cases reported, in which endometrial tissue was obtained. Then, too, there is considerable variation in the criteria for microscopic diagnosis of the endometrial hyperplasia as originally laid down by Novak,⁸ who stressed the "Swiss cheese" pattern. Of the four cases in which sections of the endometrium were present in our series, there was only one case of endometrial hyperplasia, with an associated endometrial polyp. Three cases showed typical postmenopausal endometrium.

The association of myomas of the uterus has been variously reported from 46 per cent¹⁵ to 62 per cent.^{5, 14} Uterine myomas, adenomyosis, uterine hypertrophy, and carcinoma of the endometrium has been found in association with theca-cell tumors more often than can be explained on the basis of pure coincidence. With their known estrogenic properties, this is not a surprising observation and parallels the associated findings of granulosa-cell tumors.

Examples of associated adenocarcinoma of the endometrium have been reported five times by Wolfe and Neigus,⁷ Dockerty,⁵ Geist and Gaines,⁴ and Banner and Dockerty,¹⁴ with all of these occurring in the postmenopausal age group. Primary malignancy of a theca-cell tumor with the presence of ascites and metastasis was found on one occasion by Loeffler and Priesel² and once with ascites only by Geist and Gaines.⁴ Of the fifteen cases reported here, none of the tumors showed any evidence of malignancy microscopically, and there were no cases of associated adenocarcinoma of the endometrium.

There is nothing known about the radiosensitivity of thecomas. However, the experimentally produced tumors in the mouse are radioresistant. This does not propose a major problem in treatment since there have been only two cases

The symptomatology centers around the estrogenic properties of these tumors and the symptoms produced vary according to the stage of life in which the stimulus is felt. Since 65 per cent of the reported cases are fifty years of age or more one would expect the symptomatology to manifest itself as postmenopausal bleeding. And this is actually the case and has been found to occur in approximately 65 per cent of cases. If this stimulus should occur during the reproductive life of the woman, episodes of either amenorrhea, menorrhagia, or metrorrhagia may occur, depending upon the amount of estrogenic substance produced by the tumor. The reports on derangement of the menstrual cycle are not very concise. Banner and Dockerty¹⁴ noted it in only three of six patients under 45 years, and stated that in 25 per cent of cases there are no symptoms suggestive of endocrine dysfunction.¹⁶ McGoldrick and Lapp,¹⁵ state that 65 per cent occur postmenopausally and 35 per cent between puberty and the climacterium. From the two series mentioned above and the cases reported here it can be seen that most cases occur between the fifth and sixth decade. Our figures check closely with those obtained from Dockerty,⁵ Banner and Dockerty,¹⁴ and McGoldrick and Lapp,¹⁵ being around 30 per cent occurring in the fifth and sixth decade, as seen in Table I.

TABLE I. OCCURRENCE BY DECADES OF THECA-CELL TUMORS

| AGE BY DECADE | SURVEY OF LITERATURE BY MCGOLDRICK & LAPP ¹⁵ | | DOCKERTY, ⁵ BANNER AND DOCKERTY ¹⁴ | | KNIGHT | |
|--------------------------|---|-----------------------|---|-----------------------|-----------------------|-----------------------|
| | NUMBER OF CASES | PER CENT BY DECADE | NUMBER OF CASES | PER CENT BY DECADE | NUMBER OF CASES | PER CENT BY DECADE |
| 15-19 | 3 | 4.0 | | | | |
| 20-39 | 7 | 9.4 | 1 | 4.3 | | |
| 30-39 | 8 | 10.8 | 2 | 8.7 | 2 | 15.4 |
| 40-49 | 8 | 10.8 | 5 | 21.7 | 3 | 23.0 |
| 50-59 | 28 | 37.83 | 8 | 34.8 | 4 | 30.7 |
| 60-69 | 12 | 16.2 | 4 | 17.4 | 3 | 23.0 |
| 70-79 | 5 | 6.7 | 2 | 8.7 | 1 | 7.7 |
| 80-89 | 0 | | 1 | 4.3 | | |
| 90-95 | 1 | 1.3 | | | | |
| Not stated | 2 | | | | 2 | |
| Average age in years | 50.65 | | 53.5 | | 53.6 | |
| Total number of cases | 74 | | 23 | | 15 | |

In the case of Mrs. M. E. M., who was 55 years of age, with cyclic vaginal spotting, the smear from the vaginal epithelium showed less than two plus estrogenic activity as graded by the Shorr method. However, the biologic assay revealed only 0.2 gamma of estrone in 100 Gm. equivalent of the extracted tissue. This tumor weighed 7,727 Gm. (17 pounds) and is the largest one reported to date. McGoldrick and Lapp¹⁵ reported one as weighing 5,380 Gm. which occurred in a 17-year-old girl. It should be stressed that the size of the tumor bears no relationship to the endocrine function. In our case, the tumor showed marked differentiation, with a bright yellow color and an abundance of lipid material, but the estrogenic content was low and there was no progesterone found on assay. Pregnanediol assay of the twenty-four-hour urine specimen was also negative, and no withdrawal bleeding occurred after surgery. This points strongly to the fact that the estrogen produced by these tumors is unopposed by progesterone, which may explain some of the findings reported, such as irregularities of the menstrual periods, postmenopausal bleeding, endometrial hyper-

In the experimentally produced tumors, most instances were of the so-called mixed type with both granulosa and theca-cell admixture. However, as stated above, pure types of each were also found. Traut and Marchetti⁷ found admixtures of theca and granulosa cells, reporting only four pure theca-cell tumors. Novak and Gray⁷ from the study of their cases found granulosa cells in theca-cell tumors and proposed a common origin and believe that one should not attempt too close a differentiation. Geist⁹ and most other writers maintain that they are a distinct group, as there are certain differences in occurrence, age group, chemical analysis, histology, and staining properties.

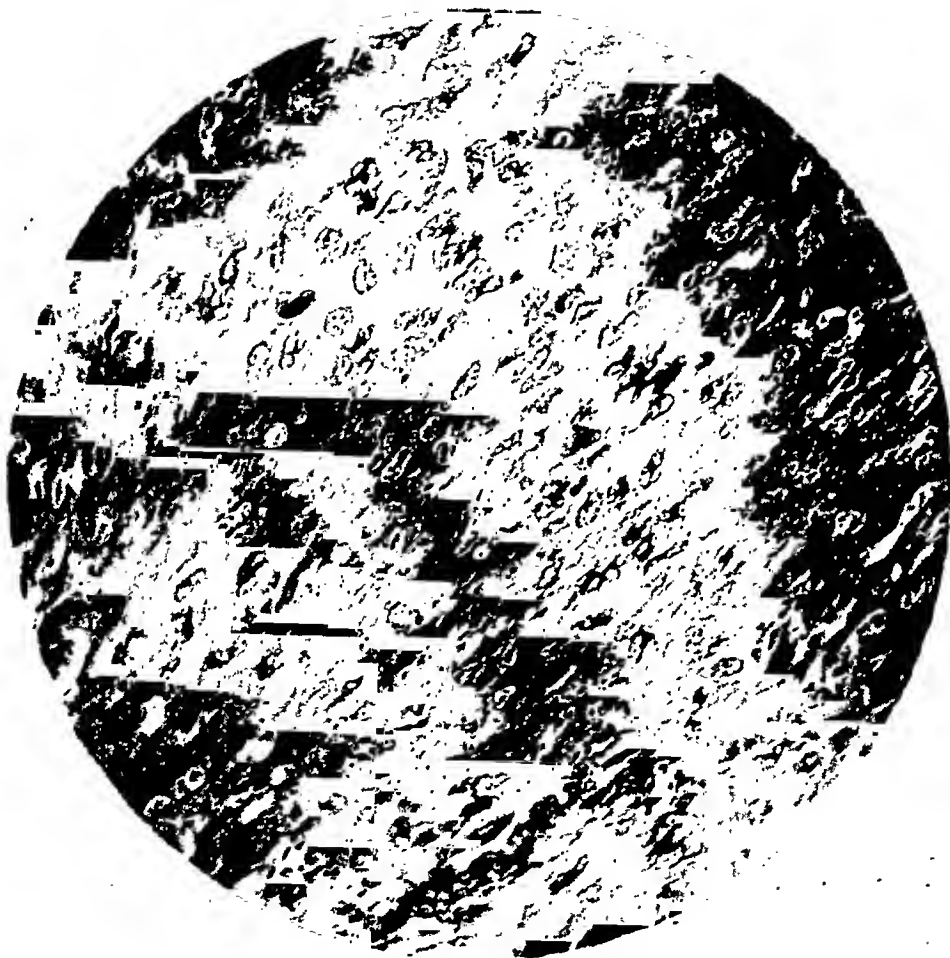


Fig. 1.—Theca-cell tumor. Hematoxylin-eosin stain. 265X magnification. The stroma is basket weave in type with spindle-shaped cells with elongated nuclei which are irregular and stain deeply.

Grossly, the tumor is white and fibrous and is usually irregular in shape. The smaller tumors usually demonstrate a capsule which may be lost when they become larger in size. They are firm, fibrous tumors and about the same consistency as a myoma of the uterus. On gross examination, one feels that he is dealing with an ovarian fibroma until the tumor is sectioned and the bright yellow color becomes apparent. This yellow color is a constant finding and the best gross diagnostic criterion. It may be necessary to allow the tumor to stand at room temperature before this yellow color makes its appearance, but it was

of established primary malignancy. Ascites is certainly no indicator of malignancy, as these tumors occasionally produce abdominal fluid and sometimes Meigs' syndrome^{17, 19} just as do ovarian fibromas.

The clinical diagnosis is difficult in the absence of vaginal bleeding, breast changes, and an ovarian tumor occurring after the menopause. The most frequent diagnosis made in our series was myoma of the uterus, and, in most instances, the tumor was large enough to palpate bimanually on pelvic examination. Some were thought to be pedunculated subserous uterine myomas because of the intermittent bouts of abdominal pain, which were interpreted as torsion of the pedicle with impairment of the circulation. The frequent association of myomas of the uterus with theca-cell tumor does not simplify the diagnosis. Pain was present and associated with an abdominal mass in four of six cases, 66 per cent, in which information was available. The tumor usually is free in the pelvis or abdomen, being attached only by its pedicle. Either ovary may be involved but in the cases so far reported there is a predilection for the right side.

The surgical procedure of choice should be dictated by the age of the individual, presence or absence of associated pathology, such as myomas of the uterus, exclusion of associated adenocarcinoma of the endometrium, and the like. A diagnostic curettage should always be done regardless of whether one does conservative or radical surgery. In the premenopausal woman, curettage of the uterus and removal of the involved ovary is adequate and safe. There is little reason for castration and hysterectomy in this type of case, without associated pathology which could warrant it on its own merit, as primary malignancy of these tumors is rare. The curettage is highly important to rule out associated adenocarcinoma of the endometrium. Even in the absence of a malignancy in the menopausal or postmenopausal woman, a bilateral salpingo-oophorectomy and hysterectomy should be considered if the condition of the patient will permit. Here the curettage should be done as the first part of the operative procedure, because the presence or absence of an endometrial malignancy will dictate the type of surgery necessary. It goes without saying that a total hysterectomy and bilateral salpingo-oophorectomy should be done if a malignancy is encountered.

Histogenesis and Pathology

These tumors are thought to be of a mesenchymal origin and to arise from cells of the theca interna of the Graafian follicle.^{1, 8} Traut and Butterworth¹ had occasion to study a group of ovarian tumors which were produced incidentally to the production of leukemia in rats and mice by 190 kw., 30 Ma. of x-ray radiation at 50 cm. distance through 0.5 mm. of copper plus 1 mm. of aluminum filtration. They found that granulosa cells are extremely sensitive to the roentgen rays, which first depressed and then stimulated growth of these cells to such a degree that tumor formation resulted. In these tumors they found granulosa-cell tumors, theca-cell tumors, and mixtures of both types. In confirmation, experimental thecomas, granulosa-cell tumors and lutein-cell tumors have been produced through radiation by Traut and Butterworth,¹ Geist, Gaines and Pollock.⁷ The atresia of the Graafian follicle produced in this way may parallel the pathogenesis of theca-cell tumors. It is known that ovaries, when grafted into castrated animals, eventually undergo follicular atresia with proliferation³ of the theca cells just like the tumors experimentally produced by the roentgen ray. That the process of follicular atresia occurring postmenopausally may set off proliferation of the thecal layer remains to be proved. Women do develop ovarian tumors following heavy radiation, as has been observed by Voght and Smith¹ and by Traut.¹

cell has a pericellular collagen reticulum which can be demonstrated by silver impregnation technique. Granulosa cells are reticulum free¹¹ but contain argen-taffin granules¹⁶ which are lacking in the theca cells. These differences, therefore, should afford a method for microscopic differentiation in doubtful cases, but we found that the method is sometimes confusing and difficult of interpretation. Foote's modification of Bielschowsky's silver stain was used in the cases

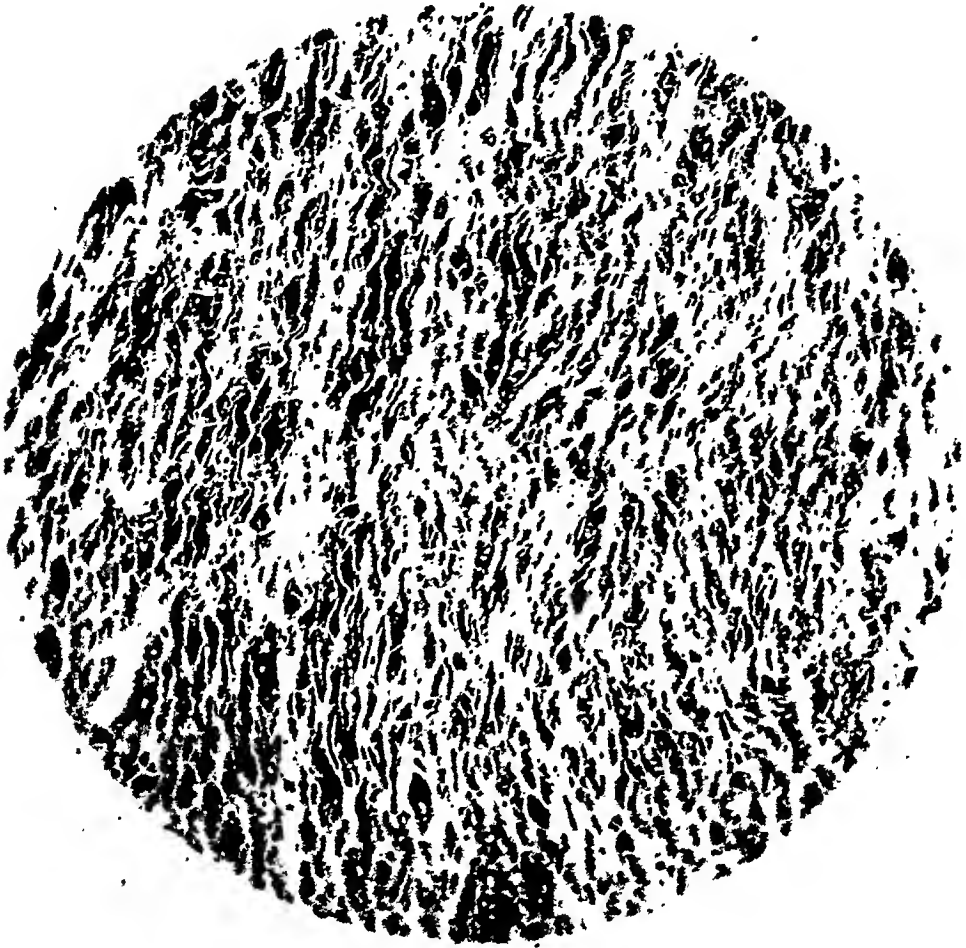


Fig. 3.—Theca-cell tumor. 265X magnification. Foote's modification of Bielschowsky's silver impregnation showing the pericellular collagen reticulum.

here reported. However, in our hands, hematoxylin and eosin and fat stains were adequate for diagnosis in most instances. Some tumors are more fibrous than others because of the variance in differentiation. These cases can be distinguished from fibromas with fatty metamorphosis by the absence of reticulum and increased density in the latter. It is thought by some¹⁰ that the age of the tumor and the estrogenic activity are in direct proportion to the cellular differentiation, the more fibrous the tumor, the less biologic activity and lipid substance. There was an abundance of lipid material present in all of the tumors of our series.

Chemical and Biologic Studies

Because of the estrogenic activity and the presence of large quantities of lipid substance, much interest has evolved around chemical, microchemical, and biologic assay. However, because of the rarity and difficulty in preoperative

present in 100 per cent of our cases. Later this color will fade. In one of our cases, the marked yellow coloration of the tumor was under suspicion as the patient had diabetes mellitus, which is often complicated by hypercholesterolemia and deposition of xanthomatotic areas. However, the diabetes was well controlled and the blood cholesterol was found to be normal.

Infarcts and degenerative cysts were present in the larger tumors, with the latter containing a clear to amber fluid. Interlacing bundles of glistening fibrous tissue are seen on the cut section with interspersed yellow areas which make up the greater part of the tumor.

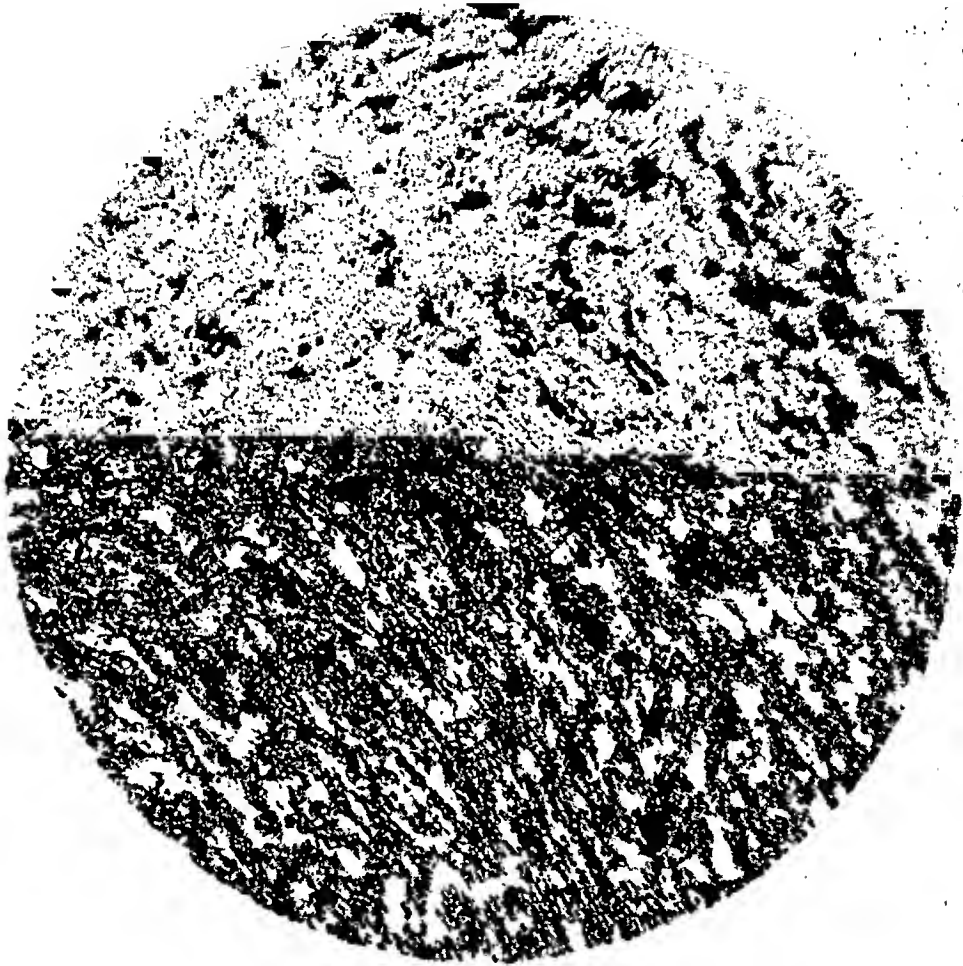


Fig. 2.—Theca-cell tumor. 265X magnification. Frozen section with Sudan IV stain showing great quantities of lipoid substance both in the cell protoplasm and lying free in the interstitial tissues.

Microscopically, the stroma is basket weave in type with elongated spindle-shaped cells with slightly elongated nuclei which are irregular and stain deeply. The cells are interlacing small islands of polygonal cells and intercellular fibrils. In frozen section with Sudan IV stain, these islands of cells contain great quantities of lipoid substance both in the cell protoplasm and lying free in the interstitial tissues. These stromal cells tend to differentiate from the mesenchymal type of connective cell by retaining their collagen fibrils but increasing in size and developing intercellular lipoid material. There are, therefore, two types of cell differentiation present, the "luteinized" and "unluteinized." The theca

between tumors having similar histologic structure and presumably similar embryonic backgrounds. The total lipid content of the tumors was only slightly more than that of the normal ovaries but there was an absolute increase of cholesterol and cholesterol esters.

Wolfe and Neigus,⁷ in their microchemical studies using Hoerr-Romeis staining technique, found a relationship between high phospholipid and cholesterol content and menstrual anomalies.

TABLE II. CHEMICAL ANALYSIS OF THECA-CELL TUMORS

| AUTHORS AND CASES | CHOLESTEROL PER CENT* | CHOLESTEROL ESTHERS PER CENT* | PHOSPHO- LIPIDS PER CENT* | TOTAL LIPIDS PER CENT* |
|-----------------------------------|--------------------------|-------------------------------------|---------------------------------|------------------------------|
| <i>Reported theca-cell tumor</i> | | | | |
| Banner and Dockerty ¹⁴ | 0.7 | 0.33 | | 2.18 |
| Average of 8 cases | | | | |
| Geist, S. H. ⁹ | 0.68 | 0.97 | 0.32 | 2.7 |
| One case | | | | |
| <i>Normal ovaries</i> | | | | |
| Banner and Dockerty ¹⁴ | 0.26 | trace to 0.13 | | 1.9 |
| Average of 7 cases | | | | |
| Hodgson et al. ²⁰ | 0.27 | trace to 0.13 | 3.65 | 1.9 |
| Average of 7 cases | | | | |
| <i>Granulosa-cell tumor</i> | | | | |
| Hodgson et al. ²⁰ | 0.52 | 0.42 | 1.26 | 1.68 |
| Average of 4 cases | | | | |

*Grams per cent.

With all available evidence at hand, it seems likely that theca-cell tumors are not as potent estrogen producers as granulosa-cell tumors.¹⁹ Early writers did not express this belief and thought the former a potent source of estrogen. They also suspected the presence of progesterone because of the great lipid content and yellow color. However, progesterone has never been reported, nor has the association of corpora lutea of the involved or opposite ovary been observed. As previously mentioned, it is not the excessive amount of estrogen but the prolonged and unopposed action that seems to produce the pathologic changes associated with these tumors.

Method of Analysis

The biological analysis was carried out through the courtesy of Drs. R. K. Meyer and W. H. McShan of the Department of Zoology of the University of Wisconsin. The tissue was refluxed for one hour with 95 per cent alcohol on the basis of 500 Gm. of tissue per L. of alcohol. The alcohol extract was separated from the tissue by filtration and the alcohol was removed from the extract under reduced pressure at 4° C. The residue remaining was dissolved in ether to which the proper quantity of oil was added, followed by heating on a hot plate to remove the ether. The oil solution or suspension of the tissue extract residue was used in testing for estrogenic and progesterone activity. The copulatory reflex method using the guinea pig was used for the progesterone assays and the weight of the uterus of the 21-day-old female rat was used in determining the estrogenic activity. The rats were castrated on the day the injections were made and one subcutaneous injection was made for each of four days, with autopsy on the morning of the fifth day. Four rats were used

diagnosis, the latter has been difficult to obtain. Therefore, only three cases are reported in the literature that had been subjected to biologic assay. Two of these showed estrogenic activity. A tumor of one of our cases was analyzed biologically and found to contain the equivalent of 0.2 gamma of estrone¹² per 100 Gm. of the extracted tissue. These estrogens were not identified. Progesterone was not present, in spite of the large amount of lipoid in this tumor. The urinary excretion of the progesterone metabolite, pregnanediol, was not



Fig. 4.—Theca-cell tumor. 265 \times magnification. Hematoxylin-eosin stain. The so-called mixed type with both granulosa and theca-cell admixture. T=theca cells. G=granulosa cells.

found in the twenty-four-hour urine specimen of this patient. Geist⁹ extracted 0.75 Gm. of tissue and by injection into mice estimated one mouse unit of estrin. Twenty-five Gm. of tumor tissue which Banner and Dockerty¹⁴ analyzed by biologic methods revealed no estrogenic substance even though the patient had experienced periodic vaginal spotting.

The lipoid substance present in these tumors for the most part is cholesterol and cholesterol esters.⁴ Microscopic demonstration of intracellular lipids is distinctive. Free cholesterol, cholesterol esters, phospholipids, acids, and neutral fat are all recognizable by the Hoerr-Romeis staining technique.⁷ This lipoid is doubly refractile.⁴ Geist⁹ points out that the lipoid in granulosa-cell tumors is phospholipid and neutral fat, while in the thecoma it is cholesterol and cholesterol esters. Banner and Dockerty¹⁴ found that chemical analyses were somewhat disappointing. They say they were unable to find any striking correlation

All laboratory studies were normal, therefore, she was operated upon June 30, 1941, through a lower midline incision. Inspection revealed a normal left Fallopian tube and ovary for her age. The uterus was found to contain multiple small intramural myomas and the right ovary was replaced by a solid tumor which was smooth, irregular in shape, firm, and apparently pseudoencapsulated. It was 20 cm. in diameter and attached to the anterior abdominal wall at one point. Operation consisted of an examination under anesthesia, diagnostic curettage, and a supravaginal hysterectomy with bilateral salpingo-oophorectomy. She made an uneventful recovery. This patient received 11 treatments of 200 r each of deep x-ray therapy because of the adhesions between the tumor and the anterior abdominal wall. The diagnosis here was thecoma of the ovary and myomata of the uterus. The endometrium was of the senile type. She was living and well on Sept. 29, 1942, with no evidence of recurrence. Microscopically, this tumor contained intra- and extracellular lipid, reticulum, and morphologically was a thecoma.

CASE 3.—Mrs. N. M., aged 58 years, hospital number 218693, was admitted on Oct. 26, 1942, for laparotomy because of an ovarian tumor discovered at a previous admission. She had two previous admissions because of an intertrochanteric fracture of the right hip and diabetes mellitus, generalized arteriosclerosis, hypertensive heart disease with cardiac enlargement, relative mitral insufficiency, aortitis, and functional capacity of II to III. She had also developed a thyroid adenoma which was mildly toxic. It was during this admission that a firm, irregular, movable mass was found in the right lower quadrant of the abdomen extending to within 2 inches of the umbilicus on the right. The liver edge was down one fingerbreadth below the costal margin but not tender and smooth to palpation. Pelvic examination revealed a lacerated and chronically infected cervix with two polyps presenting at the os. The adnexa on the right were replaced by the above-mentioned mass which was not clearly defined from the uterus. The latter was not thought to be enlarged. The left adnexa were normal. There were internal and external hemorrhoids and a large asymptomatic rectocele. There was no history of vaginal bleeding, and the menopause had been at 46 years of age without event.

She was prepared for operation after a complete study consisting of regulation of her diabetes and a careful check for metastasis as the preoperative diagnosis was a possible carcinoma of the ovary. The thyroid adenoma assumed secondary importance. She was operated upon Oct. 30, 1942, and a diagnostic curettage, cervical biopsy, cauterization of the cervix, bilateral salpingo-oophorectomy, and supravaginal hysterectomy were carried out. She made an uneventful recovery. There was no follow-up on this case.

The pathologic specimen consisted of a uterus, both Fallopian tubes, an atrophic left ovary, and a large, white, irregular, nodular tumor measuring approximately 16 by 17 by 9 cm. and weighing 1313.5 Gm. The uterus, left tube, and ovary weighed 60 Gm. and the uterus measured 5 by 4.5 by 3 cm. It was small, smooth, and the myometrium measured 1.8 cm. in thickness. The endometrium was atrophic. The tumor turned yellow on section and presented whorls of fibrous tissue. On standing at room temperature the yellow color became intense. Microscopically, much lipid was present, reticulum was present, and the microscopic appearance was that of a thecoma.

Summary

Fifteen cases of theca-cell tumor of the ovary, with a review of the literature, have been presented, with emphasis on the historical, chemical, histologic, and pathologic concepts of this neoplasm. Because of the production of estrogenic substance and the manifestation of certain hormonal changes produced by this type of "feminizing" ovarian tumor, an attempt has been made to correlate the clinical and pathologic findings. In one of our cases, the tumor was analyzed biologically and found to contain estrogenic substances. With this evidence and the experience of others^{3, 13} there remains little doubt of the estrogen-producing

on this assay. The data obtained indicate that the activity was equal to 0.2 gamma of estrone per 100 Gm. of tissue.

Five guinea pigs were used for the progesterone assay, each guinea pig receiving the equivalent of 250 Gm. of the tissue. None of the guinea pigs reacted positively. As little as 0.05 international unit of progesterone will give a positive reaction in the guinea pig. The method which was used for assaying the progesterone has been previously described.²¹

Case Reports

CASE 1.—Mrs. M. E. M., aged 55 years, hospital number 72408, gravida vii, para vi, was admitted on July 21, 1943, with the chief complaint of a tumor in her abdomen of six years' duration. During this period she had noticed an increasing fullness of her abdomen, especially in the last two years when the tumor seemed to be growing more rapidly. In the five months prior to admission her weight had decreased from 147 to 133 pounds (a loss of 14 pounds) and she had experienced increasing fatigability and cramping in both legs. Her menstrual history revealed the menarche at 14 years of age and an asymptomatic menopause at 49 years of age. In the six years since her menopause, she had vaginal spotting of blood on only one occasion. There had been no changes in her breast.

Physical examination showed a well developed and fairly well nourished white female who was not acutely ill. The physical findings were not remarkable, except the abdomen, which contained an easily palpable, firm, hard, rounded, smooth mass which arose from the left side of the pelvis and extended above the umbilicus. It was freely movable and not adherent. Pelvic examination failed to show the senile postmenopausal change of the mucous membrane and vaginal smears revealed 2 plus estrogenic activity by the Shorr method. The uterus and cervix were possibly larger than expected for her age and were separate from a large mass filling the true and false pelvis which compressed the uterus to the right. Laboratory examination of the blood and urine were all within normal limits. She was operated upon July 24, 1943, and through a lower midline incision a tumor measuring 30 by 24 by 14 cm. and weighing 7,727 Gm. was removed. It arose from the left ovary which was part of the tumor and was suspended by a pedicle. The right ovary, uterus, and Fallopian tubes were normal and were not removed. There was a slight amount of clear amber peritoneal fluid. There was no curettage done on this patient. Recovery was uneventful and she is living and well.

The specimen was a large solid ovarian tumor and the surface was smooth, being broken at only one point by a pedicle measuring 3 cm. across. Upon cut section, it revealed that about three quarters of the mass was solid, the remainder being cystic and containing clear amber fluid. The cut surface was white and composed of whorls of fibrous tissue resembling a myoma. This white color changed to a definite yellow color on exposure to the air. Microscopically, this tumor contained intra- and extracellular lipid by Sudan IV stain on fresh frozen sections. Foote's modification of Bielschowsky's stain revealed reticulum and the microscopic picture with hematoxylin and eosin was that of a thecoma. This tumor was biologically analyzed for estrogen and progesterone, and pregnanediol excretions were carried out on the urine. The results are reported herein.

CASE 2.—Mrs. E. L., aged 59 years, hospital number 221575, gravida v, para v, was admitted on June 24, 1941, with the chief complaint of pain in the lower right abdomen which had begun as a discomfort several years before, but had become a definite pain in January, 1941. Her menarche was at 13 years of age and the menopause at 50 years of age. There had been no postmenopausal bleeding. The remainder of the history was noncontributory.

Physical examination was entirely normal except for varicose veins of the lower extremities and tenderness of the right lower quadrant of the abdomen on deep palpation and a palpable, firm, nodular mass in this same area. On pelvic examination, there was palpated a firm, nodular mass filling the right adnexal region, being separate from the uterus and extending to the level of the umbilicus and over to the midline. The uterus was enlarged with multiple small myomas.

5. The collected evidence is not conclusive as to whether theca-cell tumors represent a distinct histologic type of ovarian neoplasm and the subject warrants further study, since the active endocrine principle of both theca-cell tumor and granulosa-cell tumor is estrogen.

6. Theca-cell tumors occur most frequently in the fifth and sixth decades with 61.5 per cent of our patients past 50 years of age.

7. Uterine curettage should be done in all cases to rule out associated adenocarcinoma of the endometrium.

8. Conservative surgery is the operation of choice in the premenopausal patient in the absence of associated adenocarcinoma of the endometrium. In the presence of the latter, total hysterectomy is always the procedure of choice.

9. The distinctive diffuse yellow color seen on section of theca-cell tumors is the best gross diagnostic criterion and was present in 100 per cent of our cases.

I wish to express my appreciation to Dr. William D. Stovall, Sr., of the State Laboratory of Hygiene of the University of Wisconsin for his help and guidance in preparing the material for this paper; to Drs. R. K. Meyer and W. H. McShan of the Department of Biology, University of Wisconsin for the biological analysis of the tumor presented herein; and to Dr. John W. Harris for his help in preparing the manuscript.

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capacity of these tumors. There has been increasing evidence that the estrogen is unopposed by progesterone, and that it is this prolonged stimulation which is responsible for the relatively high incidence, especially in postmenopausal patients, of associated myometrial hypertrophy, uterine myomas, endometrial hyperplasia, and endometrial carcinoma. These processes have been found in association with theca-cell tumors more often than can be explained on the basis of coincidence. We did not find progesterone in the analysis of the tumor tissue nor did we find pregnanediol in the urine of the patient.

The question as to whether theca-cell tumors contain islands of granulosa cells enmeshed in their structure is still an open one. Some believe that it is the presence of the latter which accounts for the variation in estrogenic content. However, most writers believe that theca-cell tumor is a definite entity and should be assigned its proper place among the specialized tumors of the ovary. The latter opinion has come about because of certain clinical, microscopic, and chemical differences. Granulosa-cell tumors occur before the age of puberty in some 5 to 10 per cent of the cases, while theca-cell tumors have not been so reported. There is a reticulum network in thecomas which is not present in the former tumor. Argentaffin granules are present in the granulosa cells and chemically their lipoid is phospholipid and neutral fat, while in the thecoma it is cholesterol and cholesterol esters. The commonly supposed origin of the two cell types from the ovarian mesenchyma, each having estrogenic properties, has made it difficult to determine which is the source of estrogenic production. It is known that the more fibrous the tumor, the less the hormonal activity.¹⁰

We believe that conservative surgery should be carried out on the premenopausal patient when there is no associated pelvic pathology, as primary malignancy is rare. The use of preliminary diagnostic uterine curettage on all patients is emphasized. The menopausal and postmenopausal patient should be evaluated on the general condition of the patient, the associated pathology, and the presence or absence of malignancy in determining the employment of radical or conservative surgery. In the presence of an associated adenocarcinoma of the endometrium, total hysterectomy and bilateral salpingo-oophorectomy is the procedure of choice.

Conclusions

1. Fifteen cases of theca-cell tumor of the ovary have been evaluated and presented, with a survey of the literature and a clinical and pathologic review.

2. This series contained the largest theca-cell tumor yet reported, weighing 7,727 Gm.

3. Biologic assay of this tumor revealed the equivalent of 0.2 gamma of estrone per 100 Gm. of extracted tissue. There was no progesterone in the tumor tissue and no pregnanediol excreted in the urine of the patient.

4. Although the estrogen produced by thecoma is small, its effect is prolonged and unopposed by the action of progesterone, which may account for the symptoms and frequent occurrence of associated pathology, such as menstrual irregularities, postmenopausal bleeding, endometrial hyperplasia, adenomyosis, hypertrophy of the myometrium with uterine enlargement, uterine myomas, and endometrial carcinoma.

No abnormality of the skin or visible mucous membranes could be found. Systematic examination of the head, the neck, the chest, the abdomen, and the extremities disclosed no evidence of pathologic change. The appearance of each retina was normal. The nail beds were particularly noted to be clear, and the areas of the neck, the axillae, and the groins were found to have no palpably enlarged lymph nodes.

Laboratory Studies.—The hemoglobin was 12.0 Gm.; red blood cells 4,210,000; and white blood cells 6,900, with a differential count of 65 per cent neutrophils, 30 per cent lymphocytes, and 5 per cent monocytes. The Kahn serologic test was negative, and the Rh factor test was positive. A routine urinalysis disclosed no abnormality. On Dec. 19, 1946, roentgenographic study of the chest was negative.

Later Surgical Treatment.—On Dec. 16, 1946, under cyclopropane anesthesia, excision of the tumor was performed, a portion of the underlying deep fascia and a 2 cm. margin of the surrounding normal tissue being included with the operative specimen. The wound was closed by reapproximation of the undermined mucosal edges, and an inlying urethral catheter (Foley type) was left in place to drain the bladder.

Histopathologic study of the specimen at once confirmed the clinical impression that this tumor represented a recurrent or residual melanoma. Painsstaking review of the previous sections, made twenty-eight months before, then soon led to the discovery of a tiny area of the same type of tumor tissue. Further surgical excision was immediately urged, with prophylactic groin dissection and vulvectomy in mind, and, after a week of deliberation by the patient, consent to these procedures was obtained. Repeated physical examination again disclosed no evidence of any other abnormality.

On Dec. 24, 1946, under continuous spinal anesthesia, radical dissection of both groins was carried out. The skin incision which was used began at a point about 2 inches above and 1 inch medial to the anterior superior iliac spine, then crossed the medial third of Poupart's ligament and continued to the lower border of the triangle of Scarpa. Skin flaps were reflected laterally as far as the anterior superior iliac spine and the edge of the tensor fasciae lata, and medially to the midline of the lower abdominal wall and to the adductor muscles of the thigh. The subcutaneous tissues thus laterally exposed were then dissected in one portion from the external oblique fascia, with unroofing of the inguinal canal, excision of the round ligament close to the peritoneum, and division of Poupart's ligament in the line of the incision. Mobilization of the peritoneum of the lower abdominal wall was then effected to expose the bifurcation of the common iliac vessels, and from this level outward all the overlying tissue was stripped from the iliac fossa, the obturator region, and the more important arteries, veins, and nerves. The inferior epigastric artery was deliberately sacrificed, and, in the thigh, the rectus femoris muscle was cleaned of all adherent overlying tissue. The saphenous vein was ligated and divided at the fossa ovalis, all adherent tissue was dissected upward from the femoral nerve and vessels, and medially the adductor muscles of the thigh were cleanly bared. The block of tissue thus obtained was tucked beneath the medial skin flap and left attached to the suprapubic structures until vulvectomy and a similar dissection of the other groin had been completed. Poupart's ligament was reconstructed, and a McVay hernioplasty was performed by approximating the transversalis fascia to the ligaments of Gimbernat and Poupart. A cigarette drain was placed in the femoral triangle and brought out through a stab wound on the medial aspect of the thigh. A mixture of about 4 Gm. of crystalline sulfanilamide and sulfathiazole was sprinkled throughout the wound, and the incision then was closed with interrupted, vertically placed mattress sutures of medium-sized silk. The same technique of operation was observed in the dissection of the other groin.

With the patient then placed in the lithotomy position and with an inlying urethral catheter (Foley type) inserted, vulvectomy was carried out by a technique intended to preserve the continuity of the dissection. On the left side practically all of the lateral wall of the vagina was included in the incision. Superiorly the operative field was extended to include the attached mass of tissue dissected from both inguinal regions, so that the entire specimen could be removed en masse. Closure of the defect in the walls of the vagina was effected with the flaps of tissue formed by the mobilization of the lateral and posterior walls. The vaginal wound was closed in layers with interrupted sutures of fine chromic catgut. The

PRIMARY MELANOMA OF THE VAGINA, WITH A REVIEW OF THE LITERATURE

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PPRIMARY melanoma of the vagina, known more commonly as melanosarcoma, is an ominous, extremely rare disease. Our apparently successful treatment of a patient thus afflicted now encourages the following report.

CASE REPORT.—Mrs. K. P., a white American housewife now 28 years old, was first seen as a private patient in May, 1944. She had noticed a persistent yellow vaginal discharge, occasionally streaked with blood, during the preceding ten-month period. She had also experienced pain in the vagina during coitus, and she had found occasion to attribute some degree of blood loss directly to this act.

No previous medical attention had been sought because of this complaint.

The reviews of the family history and of the past medical record yielded no contributory information. The only pregnancy resulted in the spontaneous delivery at term, twenty-eight months prior to the onset of the present illness, of a normal, living male infant which had presented by frank breech. The menstrual history otherwise was normal.

Initial Physical Examination.—No general evidence of abnormality was discovered at the initial physical examination. About 1.5 cm. within the vaginal introitus, on the midpart of the left lateral wall, was a rounded, flat, nonpigmented tumor about 2 cm. in diameter. A superficial area of ulceration, about 1.5 cm. across, occupied the central portion of its surface. The tumor seemed to be restricted to the mucous membrane layer, and gentle palpation of its edge, which elicited complaints of severe pain, readily displaced its base over the underlying tissues. No other evidence of pelvic abnormality could be found, and efforts to identify the inguinal lymph nodes by palpation were entirely unsuccessful.

Initial Surgical Treatment.—Immediate surgical excision was advised. On July 31, 1944, excision of the tumor was performed, the marginal surrounding tissue and an adjacent portion of the minor labium being included with the operative specimen. The routine histopathologic report read, "Growth from the vagina: Sections show a gland structure and old process of repair." Later discussion with the pathologist led to the verbally expressed opinion that the tumor was benign. The wound healed uneventfully, and the patient returned home on the seventh postoperative day.

Later Physical Examinations.—Further examinations were performed at two-month intervals thereafter, and for nearly sixteen months no symptoms were reported and no abnormalities were found. In November, 1946, a recurrence was discovered about 1 cm. within the vaginal introitus, just anterior to the operative scar. This tumor was also flat and rounded, measuring about 1.5 cm. in diameter and about 0.5 cm. in thickness, but on the central portion of its surface was a light bluish area of discoloration about 0.5 cm. across. There was no evident extension beyond the limits of the immediately adjacent mucous membrane. A painstaking examination of the pelvic organs disclosed no further abnormality.

A careful general examination was accordingly performed. The patient was a well-developed, well-nourished white woman, 26 years old. The temperature was 98.8 degrees F.; pulse 76; respiratory rate 20; blood pressure 130/80; height 5' 6"; and weight 115 pounds.



Fig. 1.—Photomicrograph of a portion of the tumor, showing typical spindle-shaped cells, dark-stained nuclei, and pigment granules ($\times 400$).

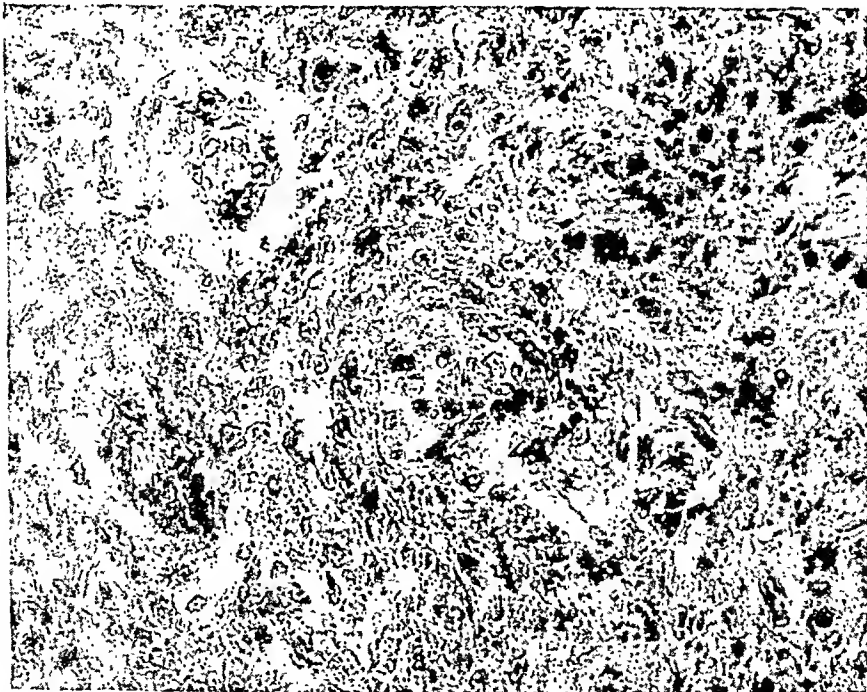


Fig. 2.—Photomicrograph of a portion of the tumor, showing details of the tumor cells and the predominantly intracellular disposition of the pigment granules ($\times 800$).

represented by the patients in this group was found to lie between extremes of 22 and 68 years. Of 9 patients who were married, 1 had been nulliparous, 2 had acknowledged 4 spontaneous abortions, and 7 had borne a known total of 27 living children. Mention of the previous occurrence of menopausal symptoms, an average of 10.9 years prior to the onset of the disease considered here, was recorded in 4 cases, but, judging from the ages given for the entire group of patients, the presence of such symptoms had presumably been noted in some antecedent period in 7 of the 13 cases. A pre-existing leucorrhea, of unknown significance, was admitted by 1 patient.

Melanomas which arise primarily in the vagina are apparently identical in structure with those which take their origin from other tissues. Their appearance histopathologically is likewise varied, though a preponderance of pigment-bearing cellular components is almost invariably noted. Following the choice of terms previously adopted by Adair and currently in common usage at the Memorial Hospital in New York, further reference to these tumors by any other designation seems to be unnecessary.

The signs and symptoms of the presence of melanomas of the vagina have been commonly reported for the great variety of new growths which develop in this site. Bleeding evident as "spotting" or as "staining" frequently occurs, and discovery of the tumor at an early date often influences the patient to seek medical attention. Other symptoms may include vague abdominal distress, leucorrhea or an increase in a pre-existent like discharge, pain or swelling in the groins, or recently occurring dyspareunia. In 10 cases with histories which were cited in detail, it was found that 4 patients had told of bleeding, 2 patients had made complaint of some abdominal discomfort, and 4 patients had learned of the presence of the tumor through palpation, while single mention of such symptoms as persistent leucorrhea, recurrent vaginal discharge, swelling of the groins, painful coitus, dysuria evidenced as burning at the time of urination, and the feeling of a lack of perineal support was recorded also for the patients of this group. An average period of three and two-tenths months had elapsed between the time of onset and that of requested medical attention, and no known symptoms in this series had admittedly persisted longer than a period of ten months. An asymptomatic tumor, in 1 of the 8 remaining patients, was discovered at the first examination after childbirth.

The point of origin of this disease in all but 2 of 13 cases had been clearly situated within the lower third of the vagina. Single tumors were described on the anterior wall in 4 cases, on the anterolateral wall in 1 case, on the posterior wall in 3 cases, and on the lateral wall in 2 cases, while in 1 case several areas of involvement were discovered on both the lower anterior and lower posterior walls. In the 2 remaining cases, showing evidence of primary abnormality in other parts of the vagina, accounts had been given of multiple, diffusely scattered, papillary outgrowths in one instance and of extensive, sloughing disease of the vaults and of the cervix in the other. Single tumors measuring 2 to 4 cm. in diameter were reported in 2 cases, while the sites affected in 4 other cases were less accurately observed to have the size of a small nut, a hen's egg, or a coin as large as our half dollar. Represented also in this group of 13 cases were 5 nodular or definitely papillary tumors, 4 sharply defined areas of plaque-shaped neoplastic growth, and 6 instances of secondary ulceration of the tumor surface. In one case, an evident thrombosis of the veins within the groin was later shown to have concealed an area of inoperable disease, but, in the other cases, no initial finding indicative of extravaginal extension of the tumor was reported.

Melanomas in this site achieve a widespread distribution, once they have surmounted the vaginal barriers to their progress. Lymph drainage from most of the upper half of the vagina, as described by Rouvière, is conducted chiefly to the lymph nodes of the external iliac vessel groups, though occasionally this

were observed. There was also some edema of the right lower leg and thigh which the patient said subsided over night. A detailed physical examination then disclosed no evidence of metastatic or residual melanoma. Permission to engage again in sexual intercourse was given, and, though the advisability of abdominal delivery in the event of pregnancy was stressed, future childbearing was strongly discouraged.

The patient is still free of the disease, eighteen months after the extensive operation and almost five years after the onset of symptoms. She experiences a normal climax during coitus, and she has fully returned to her normal active life.

Discussion

Little first-hand information about the course of this disease is at present known to have been published. Veit (1897) made note of 47 previously reported cases, 17 in children and 30 in adults, but he regarded the account which Parona (1887) had presented as the sole authentic record of the occurrence of this tumor. Subsequent announcement of a number of unchallenged, variously supported cases then was made by Matthews (1897-1898), Boldt (1906), Eggel (1906), Hinselmann (1908), Graefe (1912), Stefani (1923), Mulzer (1927), Smith and Leech (1928), Meigs (1934), Traina Rao (1934), Tscherne (1937), and Bromberg and Brzezinski (1944), but, judging from the current lack of interest in this subject, little more than passing notice was apparently attracted by this group of presentations. Perzik, in his review of the records of 862 patients with melanoma treated at the Memorial Hospital in New York, has discovered 2 undoubted instances of primary vaginal involvement, while Taylor and Tuttle (1944) previously described a case in which they concluded that the point of origin of the disease had been in the cervix or in the vault of the vagina. Adding these presumptive cases to the one reported here, melanomas of this sort have now been met with in a total of 18 patients.

The source of this disease within the primary areas of its occurrence has remained a doubtful matter. From the various explanations which have been most widely held, Ewing has selected five of the most likely parent structures: (1) mesoblastic chromatophores, (2) epithelial cells and epithelial chromatophores, (3) nevus cells within the skin and mesoblastic chromatophores within the choroid, (4) endothelial cells of nerve trunks or of blood and lymphatic vessels, and (5) chromatophores, tactile corpuscles, or nerve cells forming the end-organs of the cutaneous sensory nerves. In accounting for the neoplastic transformation which ensues, he has further implicated a variety of exciting, contributory, or predisposing etiologic factors, possibly incited by chronically repeated trauma and probably directly influenced by the sympathetic nervous system, and he has also postulated a delicately adjusted balance between the rates of melanin production and of cellular proliferation. Areas of pigmentation in the walls of the vagina, even in the lower third, are apparently not normally encountered (Smith), and sensory end-organs, such as the testicle corpuscle Meissner has described, are similarly lacking in this site (Cowdry). To our knowledge, the more common, innocent pigmented tumors, represented by the *neuronevi*, have likewise not been found in the vagina, and, in our opinion, the most likely sources of the melanomas here considered lie in embryologically misplaced chromatophores of epithelial or mesoblastic origin or in the endothelial cells of the superficial nerve or vessel trunks. The possibility of nerve involvement may be clinically suggested when the primary tumors are discovered to be painful. In opposition to such views, Novak had contended earlier that melanomas of the vagina are always secondary tumors.

Careful study of the records of the 18 cases now collected has not implicated any obvious etiologic factor. The average age of 13 patients, 8 of whom were 40 years of age or older, was noted to be 42.4 years, and the age range

Summary

A case of primary melanoma of the vagina is reported in detail. An apparent cure of the disease has been obtained eighteen months after treatment by exseision, vulvectomy, and radical dissection of both groins.

A group of 17 previously recorded cases is also reviewed, and an account of the development and course of the disease is briefly given.

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pathway is interrupted near the ureteral crossing by a solitary node or otherwise diverted to nodes in the obturator fossa or to lymph nodes of the middle retroperitoneal series. Drainage from the lower boundary of this area and from the major portion of the other half of the vagina is transported mainly to the lymph nodes of both iliac vessel groups, though by anomalous connections in the smaller tributaries some part frequently is routed to certain nodes of the broad ligament or to the lateral sacral or the promontory regions, after release from the nodules in the rectovaginal septum. Collecting channels near the cervix may join with vessels from this structure, then pass directly to the pararectal lymph nodes or to nodes of the lateral vesical and retropubic chains, while similar instances of union of the branches of the vulvar and inferior vaginal networks may provide a devious pathway to the inguinal lymph nodes. Metastatic implants in these areas, also in the viscera, were discovered in 9 patients known to have died of the disease.

A most important measure to support the diagnosis of this vaginal disease is the painstaking exclusion of all possible primary foci in the other body tissues. Pigmentation may be absent, as in the initial tumor in the case reported here, or, unless its presence has attracted more than casual attention, it may, as Horn has indicated in his careful presentation of the findings after hemorrhage in a sarcoma of the vagina, be erroneously interpreted as the melanin of melanoma. Biopsy for diagnostic study, as Adair and others have in general advised, is best accomplished by excision of the primary area of disease.

Surgical excision is also the means of treatment which has found widest support (Broders and MacCarty, Adair, Daland and Holmes, Pack and Livingston, de Cholnoky, Driver and MacVicar, Perzik). The obvious step in its performance which affords the greatest promise of control of the disease is the accompanying extirpation of the regional foci of lymph drainage (Pack, Scharnagel, and Morfit). This objective is attained in vaginal tumors of this sort by combining the excision of the primary area of disease with the procedures of vulvectomy and radical dissection of both groins. The immediate outcome in these measures, as in comparable procedures under any circumstance, depends primarily upon the operative technique and the supportive aftercare with which their application is attended. The likelihood of complications incident to such dissection is no excuse for other treatment in the absence of known spread or coexistent grave disease.

The results which have attended treatment of the melanomas by means of radium or roentgen-ray irradiation scarcely justify deliberate reliance on these measures whenever the vagina is primarily involved.

The type of treatment utilized in previous instances of this disease has been cited in the records of 12 of 17 collected cases. Simple excision of the tumor was described in 6 cases, in 5 of which the ultimate results were also noted. Uncontrollable recurrence, followed by a rapid spread, killed 4 patients less than twelve months after treatment had been given, while arrest of the disease, occurring in 1 patient, persisted for a period of four years, then was variously prolonged by subsequent excisions until the patient finally died of generalized dissemination fifteen years after the onset. A more extensive surgical procedure, attempted in another patient, was limited, because of the discovery of advanced disease at operation, to the performance of vulvectomy and incomplete dissection of one groin, then was followed twelve days later by a massive pulmonary embolus and death. Roentgen-ray irradiation, chosen as the means of treatment in a patient physically unable to withstand an operation, failed to prevent a fatal outcome eighteen months after the onset, while its administration to another patient, as a measure supplementing a previous resection of the vaginal area of disease, led to unknown results. Radium was said to have been used without success in the 3 remaining patients.

slides were smeared with secretion from the vaginal vault. These preparations were stained with hematoxylin and eosin, this stain being a personal preference and not regarded as having superior attributes to other stains that have been recommended. The chief virtue of the hematoxylin and eosin stain is its technical simplicity.

Before giving the results of the various smear examinations, it would be worth while to review briefly some of the clinical features exhibited by this group of eighteen intraepithelial epidermoid carcinomas. Twelve of the eighteen cases were entirely free from gynecologic symptoms. Of those six patients having symptoms referable to the uterus, one complained only of slightly excessive yellowish vaginal discharge. The remaining five cases complained of vaginal bleeding, which in no case was excessive or continuous, and usually it had been present for only a few days or weeks. In one case, the vaginal bleeding was thought to be postabortional, which indeed it may well have been. In another case, the bleeding was explained after operation as being due to a submucous fibroid. In the remaining symptomatic cases, there were chronic cervicitis and erosion which would perhaps be a better explanation for the bleeding than the presence of the intraepithelial carcinoma. There was certainly very little found on pelvic examination to excite the suspicion of the presence of carcinoma. In sixteen of the eighteen cases, the term carcinoma does not appear in the examiner's notes. One case was diagnosed as early carcinoma of the cervix and in a second case, the diagnoses included chronic cervicitis, leucoplakia, and possible carcinoma. In a considerable number of the cases, the cervix was described as essentially clean or showing very slight erosion. Extensive erosion, chronic cervicitis, ulceration and laceration appeared commonly as objective findings. This brief summary is given in order to emphasize the early clinical stage of these cases of carcinoma of the cervix.

Perhaps objection might be raised to the reporting of smear diagnosis in intraepithelial carcinomas if the only control as to stage rested on a positive biopsy. Positive biopsies were, of course, made in all cases. We have, however, examined either the hysterectomy or trachelectomy specimen from fifteen of the eighteen cases. Each surgical specimen has been studied by prearranged plan which will not be fully detailed in this report. It seems necessary, however, to say that the entire cervix has been embedded and each block of tissue studied according to a labeled diagram. In none of the fifteen cases so studied has the presence of infiltration been discovered. The results of study of the surgical specimens should testify to the stage of disease claimed herein, even though it must be admitted that one or more of the three cases not studied in this manner might not have been true examples of intraepithelial carcinoma, had the complete cervix been embedded.

Results of the Smear Examinations

The findings recorded below are based on the initial smears taken in each case. In fourteen of the eighteen cases, the smears taken directly from the cervix gave unequivocal cytologic evidence of the presence of carcinoma. In nine of the cases, smears of the vaginal secretion were unequivocally positive and in nine cases there was a negative result when diagnosis was based on vault smears alone.

The above results are not necessarily conclusive as regards the superiority of direct smears of the cervix versus smears of the vault secretion. They do suggest, however, that if a high percentage of positive results is to be secured from asymptomatic cases of carcinoma of the cervix, it is desirable to examine smears from both sources. Even in those cases where positive diagnoses were made from both the cervical and the vault material, it was noteworthy that the quantity of cancer cells present and, hence, the ease of diagnosis, were much

SMEAR DIAGNOSIS OF IN SITU CARCINOMA OF THE CERVIX

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IT IS readily apparent that, in recent years, more and more attention has been directed to the diagnosis of uterine cancer by the smear method. Preeminent in this field of diagnosis is the work of Papanicolaou, who not only pioneered, but also developed and refined the method. The accuracy and reliability of smear diagnosis in his hands are well recorded.^{1, 2} That skill in this form of cytologic diagnosis can be acquired by others has been amply demonstrated.³⁻⁶ It has been a uniform experience that corpus carcinoma offers more difficulties in diagnosis than does carcinoma of the cervix.

We are not familiar with any published work which deals specifically with smear diagnosis of very early or noninfiltrating carcinomas of the cervix. And yet, the ultimate usefulness of the smear method may rest in its detection of these early cervical cancers. The ability to show a figure of nearly 100 per cent accuracy in positive diagnoses of infiltrating carcinomas of the cervix does not provide definite information as to the reliability of the method in the detection of noninfiltrating carcinomas. One feels reasonably assured that, in the various series of cases reported, the vast majority of these carcinomas of the cervix would have been, or had already been, detected through the ordinary means of biopsy. It is not a present purpose to debate biopsy *versus* smear diagnosis. Certainly, for an indeterminate period, the chief reliance in most clinics must be placed on biopsy. From past experience, it is assured that biopsy will disclose certain tumors which will not be diagnosable on an initial smear examination, and it must be appreciated that the reverse may be true. The problem remaining is to ascertain whether or not smear diagnosis is a useful supplementary tool in disclosing the presence of a clinically unsuspected carcinoma of the cervix.

Present Study

For about two and one-half years, smears have been collected from cases of intraepithelial epidermoid carcinoma of the cervix. Other terms employed for this lesion include carcinoma in situ, noninfiltrating carcinoma, incipient carcinoma, or preinvasive carcinoma. All of these terms have precisely the same significance and should not be a source of terminologic dispute. The cases to be reported have come from two sources, the Strang Prevention Clinic and the Gynecologic Service of the Memorial Hospital.

Due to the fact that intraepithelial carcinomas may be extremely limited in extent, it seemed reasonable to speculate that correspondingly few cancer cells might appear in the vaginal secretion. In the hope of partially offsetting this possibility, it was determined to try to increase the total take of cells by securing smears directly from the cervix itself. This was done by swabbing the cervix with a cotton-tipped applicator and then smearing the material secured on a glass slide. In all cases reported here, two slides were prepared from the material obtained directly from the cervix and for purposes of comparison, two

measure. At the present time, we are not familiar with any comprehensive study which supplies a lucid answer to this problem. Actually, the use of the smear methods under discussion occupies precisely the same position in detection clinics as it does in a program of screening population groups as a public health measure. The writers do not have any concrete information to present and yet it may not be amiss to point to some of the practical obstacles that such a program must meet. What is the incidence of carcinoma of the cervix in the female population at large over the age of 35 years? Two sources of aid were enlisted in order to secure a working figure for this question. Dr. Morton L. Levin, of the New York State Division of Cancer Control, and Mrs. Ruth Salt of the Department of Statistics, Memorial Hospital, independently estimated that in the female population at large one would expect approximately one case of carcinoma of the cervix per fifteen hundred women over the age of 35. Using this figure as a working basis and acknowledging that not all of these cases would be of an asymptomatic type, one is left with something to ponder. In order to detect one case of carcinoma of the cervix, it will theoretically be necessary to make fifteen hundred smear examinations. Certainly no fewer than two slides per case should be examined. Hence three thousand smeared slides must be studied and one could scarcely allow less than ten minutes per slide for the microscopic examination. Be well assured that it is the negative slide that consumes the examiner's time. On the basis of the preceding figures, it would require five hundred hours of microscopy to detect one carcinoma of the cervix from the general population of women 35 years of age and over. Furthermore, one oversight theoretically means that five hundred hours at the microscope have been wasted. If the proposition is offered to pathologists in these terms, many would quite justifiably resist the procedure. A pathologist would have to consent to the giving up of approximately 20 per cent of a normal working year of 300 eight-hour working days. The practical figure of economies is bound to enter the scene. The time of the pathologist is not all that is expended, inasmuch as a significant amount of the clinician's time and that of other medical attendants must be spent and the technical preparation of the material for study has to be considered. If only a rough estimate of cost is made, one must theorize that it will cost several thousand dollars per case of carcinoma of the cervix discovered, when dealing with the female population at large over the age of 35. If an inquirer would ask directly the pathologist and other participants if they are willing to devote so large a portion of time to the investigation of sterile material, it is likely that he would receive many refusals. Perhaps it would be better to skirt the difficult issues as just outlined and make an effort at solution by proposing an alternate possibility. Would it be possible to transfer from the relatively small numerical body of pathologists the chief burden of time-consumption? Would the smear method of diagnosis be more feasible if talented technical personnel could be trained to screen negative material in an efficient and reliable manner? This proposal is by no means original with the authors, since it has come from various sources and we have heard many conversations among colleagues as to the practicality of this plan. At the present time, it is probably premature to undertake a final determination of certain aspects in the pre-

greater in the slides prepared from material secured directly from the cervix. There was one exception to this general rule. In none of the cases studied in this series was the vault material positive when that from the cervix was negative. We have studied a considerable number of simultaneously taken direct cervical and vault smears from cases of fully developed infiltrating epidermoid carcinoma. Whereas, in this material the direct cervical smears contained more copious numbers of cancer cells as compared with the vault material, the source from which the material was taken was of minimal importance inasmuch as the cancer cells were so numerous that diagnosis was easy enough, regardless of whether one examined cervical or vault material. Positive results might be further increased in very early cases if one could routinely examine not only direct cervical and vault smears, but also smears taken from the endocervical canal. The ability to secure this latter source of material, however, is dependent upon a suitable anatomical presentation. If an observer is unaccustomed to the examination of smears made directly from the cervix or endocervix, it is necessary to caution that the cytology differs somewhat from the conventional vault smears, since there is a smaller percentage of squamous cells. One also finds an appreciable number of cylindrical cells as well as cells in varying stages of squamous metaplasia. These latter cells need not serve as a source of confusion if one adheres rigidly to the cytologic traits of cancer cells, details of which need not be repeated here, having been amply described in a considerable literature. To sum up, it is recommended that efforts be made to secure as large a number of cancer cells as possible in smears taken for the purpose of the diagnosis of early carcinoma of the cervix. Naturally, considerable individual variation in skill of interpretation will exist, and any means that can be added to increase ease of diagnosis should be of distinct value.

Comment

With increasing interest in the establishment of tumor clinics, variously described as prevention or detection clinics, it is becoming more than ever necessary to study and to evaluate any method that may be of aid in the diagnosis of cancer in its early stages. It goes without saying that the detection of cancer in such clinics must concern itself principally with the recognition of malignant lesions prior to the onset of symptoms, since it must be presumed that the proper function of these clinics is the examination of symptom-free applicants. The major forms of cancer that are readily detectable in an early stage are not very numerous, but among them carcinoma of the cervix occupies one of the chief positions. One of the outstanding attributes of carcinoma of the cervix is its unique diagnosability if clinical alertness is combined with proper cytologic and biopsy methods. One could, indeed, submit a brief to the effect that practically every case of carcinoma of the cervix could be detected at a stage when the disease actually did not constitute a threat to life. Specifically, carcinoma of the cervix in almost every case should be recognizable prior to the stage of infiltration. This recognition, it must be borne in mind, will not be a visual one nor will it depend upon any other type of strictly clinical examination. It means the almost universal application of cytologic study by either or both the smear methods and biopsy.

Already one has heard the question raised as to whether or not smear methods in the diagnosis of carcinoma of the cervix could be profitably applied to the screening of the female population at large as a public health detection

RETREATMENT OF THE PREGNANT WOMAN FOR SYPHILIS FOLLOWING PENICILLIN

Is Additional Therapy Necessary When Effective Treatment Has Been Given Prior to Conception?*

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WHETHER the woman who has been treated with penicillin for syphilis should be retreated when she becomes pregnant depends upon the demonstration that penicillin alone or in combination with other drugs will completely cure syphilis in the sense of eradicating the disease from the body. Since the majority of syphilitic pregnant women have a latent or late infection, this problem must be studied not only for symptomatic early syphilis but for the other stages of the disease as well. Reports to date largely concern penicillin therapy of primary or secondary syphilis in the pregnant woman. An answer to this question using one type of treatment or during one stage of the disease will not necessarily be applicable to other situations. While it is well known that the likelihood of giving birth to a diseased child when the pregnant syphilitic woman remains untreated diminishes with the duration of her infection and with the amount of antecedent therapy, an infected fetus may result as long as *Spirochaeta pallida* remains active in her body. It is for this reason that a study of the ability of the woman who has had syphilis to give birth to healthy children in pregnancies following the completion of treatment is one of the best tests of cure of syphilis we have and one of the most valuable methods of evaluating the effectiveness of any new type of therapy for this disease. Nonetheless, as preventative treatment of the syphilitic pregnant woman during pregnancy has improved gradually until under ideal circumstances it approaches almost 100 per cent satisfactory results, so, with the use of penicillin, has the risk of specific treatment to the expectant mother diminished almost to the vanishing point.^{1, 2, 3} The dictum "if in doubt, treat" has become even sounder advice with the passage of time and a more and more firmly established practice.

*Assisted by the Squibb Fellowship in Chemotherapeutic Research.

ceding discussion. With many participants already active in the field, it seems prudent to await more direct testimony from reliable sources as experience is developed.

If smear diagnosis of uterine cancer is undertaken on a wide scale throughout the nation, obviously much of its fate will depend upon the various skills developed. Acuteness in cytologic diagnosis is not subject to easy standardization. Promotion of the use of the smear method is apt to originate from persons who are not going to do the actual work. These people are not characteristically patient and do not uniformly realize that time, material, and experience are required by the cytologist before he is competent to express reliable opinions. The quicker a laboratory is rushed into diagnostic work of this sort, the quicker will damaging reports be forthcoming. Multiple training centers having skilled personnel and concentrations of material may well play a useful role in establishing the future position of this form of laboratory diagnosis. In a certain measure, individuals, institutions, and public health agencies will have to shape their own destinies according to the means at their disposal and according to the personnel that can be activated in the propagation of the method. Certain of the objections that have been and will be raised against smear diagnosis are traced to the reporting of false positives. The frequency of false positive reports will unquestionably vary from laboratory to laboratory. If these become very numerous, enthusiasm will be dulled and distrust will be cultivated. With proper mastery of the smear technique, false positives should constitute an extremely small percentage of reports. On thoughtful analysis, a false positive smear report should never lead to a surgical or radiotherapeutic disaster. In order to insure protection of all interests, a uniform rule could be adopted that a positive smear report for the presence of uterine cancer constitutes nothing more than an obligatory invitation to secure a positive biopsy or curettage before any major surgical or radiotherapeutic measures are instituted. If initial efforts at biopsy are negative, periodic follow-up smears at close intervals should be recommended. Certainly, it must be a rare uterine carcinoma that progresses to the stage of being a major threat to life when these procedures yield repeatedly negative results.

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clear the body of the mother of *Spirochaeta pallida*, not the serologic response per se, is of first importance.

Using penicillin, either alone or in combination with other drugs, we probably have a better chance of freeing the body of *Spirochaeta pallida* than ever before. With the evaluation of the results of this type of treatment, we may be able to say for the first time that it is unnecessary to retreat the syphilitic woman in subsequent pregnancies. Until a substantial series of cases has been collected, however, no such statement can be made. In order to obtain at least a partial answer to this question, we have refrained, under the following circumstances, from treating the pregnant woman who had previously received penicillin for syphilis:

1. *The woman was treated for symptomatic early syphilis and had a normal clinical and serologic response.* By this we would consider that the lesions healed and did not recur; that the blood serologic reaction became negative and remained so, or that, using quantitative titrated tests, it was progressing normally toward negativity; that the spinal fluid examination was negative.

2. *The woman was treated for latent syphilis, showed no evidence of progression of her disease, maintained a negative spinal fluid, and became seronegative or retained, quantitative tests being performed in the same laboratory, a sustained constant titer of syphilis reagin, minor day-to-day fluctuations being considered unimportant.*

3. *The woman was treated for symptomatic late syphilis and sustained a normal response, depending upon the type of disease present.*

Material*

Our personal observation of syphilitic women not retreated during their pregnancy consists of 65 patients, 52† of whom have come to term. The remaining 13 are still in the antepartum period, at the time of this report. Of the women who have delivered, 48 are Negro and 4 are white. Twenty of the women were treated with penicillin for syphilis during a preceding pregnancy, not during the pregnancy considered in this analysis. Thirty-two of the women had been treated for syphilis prior to conception, this being the first pregnancy since penicillin therapy was given. For stage of disease at time treatment was given and outcome of pregnancy see Table I.

The mothers had received various types of preconceptional penicillin therapy within certain limitations. Twenty-six of the mothers had received 1.2 million Oxford Units total dose of penicillin, eighteen had received 2.4 million units, eight had received greater amounts than this. Treatment had

*In addition to the syphilologic and pediatric care of the patients as indicated in the authorship, the Departments of Gynecology and Obstetrics of the Hospital of the University of Pennsylvania and the Philadelphia General Hospital performed the antepartum and postpartum general obstetric care of the mothers; roentgenograms of the long bones were performed as necessary by the Departments of Radiology of the two hospitals and quantitative titrated blood serologic tests were carried out by Mrs. Verna Mayer Stein in the Laboratory of the Syphilis Clinic, University Hospital and in the Division of Laboratories, Philadelphia General Hospital, under the supervision of Dr. S. Brandt Rose. Miss Emily Stannard, Senior Statistical Clerk of the Institute, assisted in the compilation of the statistical data, and attendance follow-up was performed by the public health nursing staff of the Institute under the direction of Jane Barbara Taylor, R.N.

†Of these 52 women in this study who were referred to the Institute for the Study of Venereal Disease 19 reported initially to the University of Pennsylvania, 17 to Philadelphia General Hospital, 9 to the Pennsylvania Hospital, one to Lankenau Hospital, one to Woman's Hospital and 5 to private physicians.

The biggest problem underlying the consideration of retreatment in each subsequent pregnancy of the woman who has had syphilis is in establishing the criteria of cure. In the individual case, this cannot always be based upon clinical or serologic response, or upon the duration of the disease at the time pregnancy occurs, even though these are the principal measuring sticks available to us. If the amount and type of treatment prior to pregnancy are used as our criteria, then prolonged observation, in the magnitude of twenty years, to carry the woman through her childbearing age, is necessary before one can say with certainty that the new type of treatment under consideration results in a given percentage of healthy children and a probable percentage of failures. Not until a treatment for syphilis is developed, which, when carried out, will result in cures approaching one hundred per cent in the nonpregnant cases, can the question of retreatment in subsequent pregnancy be discarded, provided, in addition, of course, reinfection has not occurred prior to conception or even during the early months of the succeeding pregnancy.

In view of the fact that, with the relatively recent introduction of penicillin, we are still basing our conclusions as to its value in the treatment of syphilis on immediate clinical and serologic response rather than on prolonged observation, it might be well to consider some of the reasoning which made previous writers so conservative in their recommendations concerning the retreatment of the syphilitic woman during pregnancy. It has been possible, since the first available data, involving various types of preconceptual antisyphilitic therapy, to find selected cases in which the previous treatment had been apparently adequate to prevent infection of the fetus without retreatment during the mother's pregnancy.

In the arsphenamine-bismuth era, the combined reports of Birnbaum,⁴ Cole and the cooperative clinical group,⁵ McKelvey and Turner⁶ and Rattner⁷ contain more than 150 cases of syphilitic women who have gone through their pregnancies untreated and have given birth to healthy children as a result of adequate preconceptual therapy. Moreover, in these selected groups, not a single syphilitic infant resulted when treatment was withheld in subsequent pregnancies. Even in the face of such data, however, we find that when we are forced to base the management of the individual case on the usual criteria, namely, a clinical and serologic evaluation, the decision may not always be easy. Thus, in the 1934 cooperative clinical group study "Syphilis in Pregnancy" (Cole as spokesman⁵), it was found that "of 107 mothers who had been serologically negative for at least one year before delivery, in three instances a syphilitic child was born, one two years after the date of infection, one four years after, and one five years after. In each of these cases, the mother's Wassermann, following the birth of the syphilitic child, reversed from negative to positive." Was this reactivation of the old infection or reinfection? Probably it was the former. They continue, "In a group of 76 of these 107 mothers, where an apparently nonsyphilitic child was born, the mother's negative Wassermann in five instances reversed to positive, the time since the infection being 2 to 4 years in 3 cases and 5 to 6 years in 2 cases." No observation could point out more clearly the lack of value of the immediate clinical response in determining the likelihood of the individual syphilitic woman's giving birth to a healthy child or serve better to emphasize the fact that the ability of the treatment given to

therapy. Nineteen were followed for periods of from one to two years; twenty-five for periods of from two to three years, and one for more than three years (37 months). Twelve of the fifty-two mothers were still seropositive at the end of observation; forty were seronegative. Of the twelve seropositive cases, six had been treated originally for symptomatic early syphilis and had been observed for 345, 349, 403, 462, 696 and 753 days, respectively, post penicillin. Four of the cases seropositive at the end of observation had been treated originally for early latent syphilis and had been followed for 430, 525, 634 and 845 days, respectively. The remaining two cases had been treated for symptomatic late (central nervous system syphilis) and observed for 762 and 822 days, respectively, after initiation of therapy.

Outcome of Pregnancy in Mothers Treated With Penicillin for Syphilis Prior to Conception Only

The 52 mothers treated with penicillin for syphilis prior to pregnancy but not during pregnancy gave birth to 46 apparently normal healthy children, with three abortions, one miscarriage, one stillbirth and one neonatal death (a premature infant who died at the age of two days). In none of the six unsatisfactory pregnancies could death of the fetus be attributed definitely to syphilis. Between 11 and 12 per cent unsatisfactory termination of pregnancy is not abnormally high for the type of patient with whom we are dealing, irrespective of syphilis. Five of these mothers were seronegative at the time of delivery but one was seropositive. The three abortions occurring in the first half of the pregnancy were in a period in which syphilis is seldom the cause of fetal death; the miscarriage was at about five months. The seropositive mother who was in this group had an abortion at three months, 340 days after receiving 2.4 million Oxford Units sodium penicillin in nine days. Her quantitative titrated blood serologic reaction, which was 128 Kline units at the time of delivery, became negative one month thereafter and remained so to 582 days post penicillin, the time of her last visit. The still birth occurred at home 772 days after penicillin treatment and no autopsy was performed. The mother had had a normal response to therapy and was still clinically normal and seronegative 906 days after treatment. The premature infant which died as 2½ pounds in weight. There was no gross evidence of syphilis but no autopsy was performed. The mother had been treated with 1.2 million units total dose of aqueous sodium penicillin fourteen months before and is now seronegative and clinically normal without additional therapy 924 days after treatment. It is of some interest, perhaps, that abortions, miscarriage, stillbirth, and neonatal death all occurred in mothers originally treated for symptomatic early syphilis. Since subsequent observation of these mothers has indicated normal response to treatment in each instance and since the circumstances of delivery did not establish any definite indication of syphilis, we feel that this is probably an incidental relationship and not significant.

Of the living infants, 45 were seronegative at the time of delivery and one was seropositive. The seropositive infant showed 1 Kahn unit only in the presence of a persistent high titer (128 units) in the mother. This positive reaction in the infant became negative almost immediately. The infants have all remained normal to physical examination, serologic tests have remained negative, and roentgenograms of the long bones have been normal. The period of observation of the infant has been less than two months in 20 instances, between two and six months in 6, between six and twelve months in 8 and more than one year in 12. In the infants studied for less than two months the diagnosis of normal is presumptive only, since they have not been followed

been given over periods of from four to twelve days, for the most part from eight to ten days. Forty-nine had received aqueous penicillin in dosage of 25,000 to 40,000 units every three to four hours. Three had received amorphous calcium penicillin in oil beeswax in total dose of 4.8 million units over a period of nine days. It was not the rule to use adjunct metal chemotherapy in these cases, but sixteen of the patients had received some arsenical or bismuth in addition to the penicillin. There was no indication that the differences in treatment outlined modified the over-all results.

TABLE I. ANALYSIS OF OUTCOME OF PREGNANCY AND OF SEROLOGIC STATUS OF MOTHER AT TIME OF DELIVERY BY STAGE OF THE DISEASE AT THE TIME OF TREATMENT IN SYPHILITIC WOMEN WHO RECEIVED PENICILLIN THERAPY BEFORE CONCEPTION BUT WHO WERE NOT RETREATED DURING THE PREGNANCY

| | STAGE OF SYPHILIS IN THE MOTHER AT THE TIME OF TREATMENT | | | TOTAL |
|--|---|-----------------|---------------------|-------|
| | SYMPTOMATIC EARLY | LATENT EARLY | SYMPTOMATIC LATE | |
| | NUMBER | NUMBER | NUMBER | |
| 1. Serologic status of mother at time of delivery | | | | |
| a. positive | 11 | 4 | 1 | 16 |
| b. negative | 28 | 6 | 2 | 36 |
| Total | 39 | 10 | 3 | 52 |
| 2. Outcome of pregnancy | | | | |
| a. full term alive | 33 | 10 | 3 | 46 |
| b. abortion | 3 | 0 | 0 | 3 |
| c. miscarriage | 1 | 0 | 0 | 1 |
| d. stillbirth | 1 | 0 | 0 | 1 |
| e. neonatal death | 1 | 0 | 0 | 1 |
| Total | 39 | 10 | 3 | 52 |

At the time of delivery some of the mothers were seropositive, others seronegative; 16 of the 52 mothers had positive blood serologic reactions when their children were born, the remaining 36 were negative (Table I). Stage of the disease at the time of initial therapy made no difference to the serologic response in this small group: about one-third in each of the three categories listed remained seropositive. Of the patients still seropositive at delivery, eight had had 1.2 million units total dose of penicillin, five had received 2.4 million units total dose, and three had received greater than 2.4 million units. Since larger numbers of women had received the smaller dosages of penicillin as given in a preceding paragraph, there is no indication that, within the limitations of this study, increasing the total amount of penicillin given improved the serologic response.

The mothers reached term at varying intervals after their penicillin therapy. Eleven of the mothers were delivered within one year after their penicillin treatment. Five of these were seropositive at delivery. Thirty-one gave birth to their children between one and two years after treatment; ten of these were seropositive. Ten of the mothers were delivered more than two years after their penicillin therapy. Only one of these was seropositive. The duration of observation after treatment is accordingly a more important factor in determining the serologic status at the time of delivery than is either stage of disease or size of dose of penicillin within the limitations we have employed.

The average duration of follow-up of the mothers after penicillin treatment was twenty-seven months. Seven were followed for less than one year. One of these mothers died at 360 days from causes unrelated to syphilis or penicillin

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long enough to rule out syphilis satisfactorily. The infants who have been followed from two to six months we believe have had the disease reasonably satisfactorily excluded, and those followed for six months or more may be considered to be definitely normal.

Discussion and Summary

In a group of 52 mothers treated with penicillin for syphilis before but not during pregnancy, no syphilitic infants have been detected. Speiser et al.,³ in their recent publication, found one syphilitic infant among 84 similarly studied pregnancies. This analysis accordingly confirms their findings. Their syphilitic infant occurred when a mother who delivered nine months after being treated for symptomatic early syphilis was not adequately observed during pregnancy and was subsequently found to have an abnormal response to therapy. Under the ideal antepartum care which dictates monthly physical examination and blood serologic test for the woman once syphilitic, it is apparently safe to permit the expectant mother to go untreated during her pregnancy, assuming normal response to treatment as outlined in a previous section of this article. Retreatment of the syphilitic pregnant woman should be instituted where the clinical or laboratory response is not normal, or under circumstances where there is some risk of infection of the fetus and anticipated antepartum care may fall below the optimum.

We do not feel that final conclusions can be drawn from a short period of observation of the limited material collected from individual centers, but we hope that such a report may serve as a stimulus to the collection of additional data from other sources which in the aggregate may give a definite and final answer to the question of retreating the syphilitic woman because of pregnancy, when she has had an acceptable course of penicillin for this disease prior to conception.

Conclusions

1. When 52 women were treated for syphilis with penicillin before but not during pregnancy, 46 apparently normal and no syphilitic living infants resulted.
2. The three abortions, one miscarriage, one stillbirth, and one neonatal death which occurred could not be attributed to syphilis, and probably resulted from other causes.
3. So far as can be told from a limited series of cases, retreatment during pregnancy for syphilis is unnecessary, provided the expectant mother's response to previous penicillin therapy has been normal and reinfection has not occurred.
4. Criteria are given for the selection, based upon clinical response, of patients in whom retreatment for syphilis because of pregnancy may be unnecessary, but the possible fallacy of basing judgment solely on the clinical response in the individual case is pointed out. The great effectiveness and relative safety of penicillin to prevent congenital syphilis make retreatment of the pregnant woman desirable if there is any doubt whatever of the effectiveness of her previous antisyphilitic therapy.

TABLE I. CHARACTERISTICS OF MENSTRUAL CYCLES AND OF OVULATIONS OF A SERIES OF 46 WOMEN HAVING CONCEPTIONS WHICH RESULTED WHEN EITHER INTERCOURSE OR ARTIFICIAL INSEMINATION WAS PRACTICED ON THE DAY OF OVULATION, AS PREDICTED BY THE RAT TEST

| SERIAL NO. | MENSTRUAL CYCLE | | | OVULATION | | |
|------------|-----------------------------|----------------|---------|------------|-------|-------------------------|
| | STUDIED PRIOR TO CONCEPTION | AVERAGE LENGTH | RANGE | CONCEPTION | RANGE | POST-OVULATORY INTERVAL |
| | NO. | DAYS | DAYS | DAY | DAYS | DAYS |
| 1 | 1 | 25 | 23-27 | 8 | ---- | 17 |
| 2 | 1 | 25 | 21-32 | 9 | 8-9 | 16 |
| 3 | 3 | 26.3 | 25-28 | 9 | 9-11 | 17.3 |
| 4 | 0 | 24.5 | 24-25 | 10 | ---- | 14.5 |
| 5 | 1 | 25.8 | 25-27 | 10 | 10-11 | 15.8 |
| 6 | 4 | 26.9 | 25-31 | 10 | 10-12 | 16.9 |
| 7 | 3 | 24 | 23-35 | 11 | 11-11 | 13 |
| 8 | 3 | 24.3 | 21-27 | 11 | 9-11 | 13.3 |
| 9 | 2 | 25 | 25-25 | 11 | 11-13 | 14 |
| 10* | 2 | 25.5 | 25-26 | 11 | 11-13 | 14.5 |
| 11† | 9 | 25.8 | 24-28 | 11 | 11-15 | 14.8 |
| 12 | 4 | 26 | 24-28 | 11 | 10-12 | 15 |
| 13† | 3 | 26 | 24-32 | 11 | 11-18 | 15 |
| 14 | 5 | 26 | 25-27 | 11 | 11-14 | 15 |
| 15† | 6 | 26.3 | 21-33 | 11 | 6-11 | 15.3 |
| 16* | 3 | 27 | 25-29 | 11 | 11-12 | 16 |
| 17† | 10 | 27.2 | 26-31 | 11 | 11-16 | 16.2 |
| 18† | 3 | 28 | 25-29 | 11 | 11-13 | 17 |
| 19 | 4 | 23.5 | 20-25 | 12 | 11-13 | 11.5 |
| 20† | 8 | 25 | 19-28 | 12 | 11-14 | 13 |
| 21 | 2 | 26.5 | 26-27 | 12 | 10-14 | 14.5 |
| 22 | 15 | 26.6 | 25-30 | 12 | 10-12 | 14.6 |
| 23 | 4 | 27 | 25-29 | 12 | 10-14 | 15 |
| 24* | 15 | 27.6 | 25-32 | 12 | 10-16 | 15.6 |
| 25 | 5 | 28 | 27-31 | 12 | 12-16 | 16 |
| 26 | 3 | 27.5 | 27-29 | 12 | 11-17 | 15.5 |
| 27† | 12 | 29.2 | 27-33 | 12 | 12-15 | 17.2 |
| 28 | 0 | 32 | 27-39 | 12 | 12-16 | 20 |
| 29 | 1 | 26 | 24-28 | 13 | ---- | 13 |
| 30* | 1 | 27.4 | 26-32 | 13 | 13-14 | 14.4 |
| 31 | 2 | 26.5 | 25-28 | 13 | 10-13 | 13.5 |
| 32* | 4 | 26.5 | 26-27 | 13 | 12-13 | 13.5 |
| 33 | 0 | 27 | 25-29 | 13 | ---- | 14 |
| 34 | 2 | 27 | 25-29 | 13 | 13-16 | 14 |
| 35 | 10 | 27.2 | 23-30 | 13 | 11-18 | 14.2 |
| 36 | 3 | 28 | 27-28 | 13 | 12-16 | 15 |
| 37† | 5 | 25.8 | 24-30 | 14 | 11-16 | 11.8 |
| 38 | 5 | 26 | 25-30 | 14 | 12-14 | 12 |
| 39 | 11 | 28.5 | 25-35 | 14 | 11-17 | 14.5 |
| 40 | 2 | 30 | 27-33 | 15 | ---- | 15 |
| 41 | 2 | 31.5 | 31-32 | 15 | 14-18 | 16.5 |
| 42 | 2 | 29.5 | 29-30 | 16 | 15-16 | 13.5 |
| 43* | 4 | 30 | 27-32 | 16 | 16-17 | 14 |
| 44 | 1 | 32 | 27-39 | 16 | 16-16 | 16 |
| 48* | 5 | 35 | 32-37 | 16 | 16-19 | 19 |
| 45 | 2 | 29.5 | 27-32 | 17 | 17-19 | 12.5 |
| 46 | 6 | 29.6 | 28-32 | 17 | 15-20 | 12.6 |
| 47 | 0 | 33.6 | 31-40 | 17 | ---- | 16.5 |
| 49* | 0 | 32 | 30-33 | 19 | ---- | 13 |
| 50* | 1 | 32 | Unknown | 19 | ---- | 13 |
| Total | 200 | | | | | |
| Averages | | 27.6 | | 12.7 | | 14.8 |

* = Anonymous donors.

† = Homologous donors.

THE PREDICTION OF THE DAY OF HUMAN OVULATION BY THE RAT TEST AS CONFIRMED BY FIFTY CONCEPTIONS*

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RECENTLY the author described a method for detecting the time of ovulation in women¹ and in monkeys.² In a later communication Murphy and Farris³ indicated the practical value of the test, in a report upon ten women, who conceived when either intercourse or insemination was practiced on the day of ovulation, as determined by the test.

The present report deals with the time in the menstrual cycle that ovulation takes place. The observations were made chiefly upon women who had never conceived. The data upon their ovarian activity are presented.

Material and Methods

A series of 208 tests was made upon 46 individuals.

The technique employed in detecting ovulation, previously described in detail (Farris¹), is briefly as follows:

The occurrence of human ovulation is detected by the reaction of the immature rat's ovary to the hypodermic injection of the urine of the patient. If the patient's ovulation is not taking place, her urine has no effect upon the ovary of the rat. On the other hand, if ovulation is taking place, the urine injected into the rat produces hyperemia of the animal's ovaries.

Ovulation time was tested, in the average subject, for two to three consecutive months. No attempt at conception was advised on the day of ovulation during the first, or control, month. This test was made in order to determine whether it took place; whether the activity was normal or abnormal; and if normal, where in the menstrual cycle it occurred.

Intercourse was advised, or artificial insemination was performed, on the day of ovulation of the first month in which a normal ovulation reaction occurred, with the exception of the control month.

Results

The 46 patients became pregnant. Four did so twice, giving a total of 50 conceptions.

Data upon the menstrual cycles which preceded the conceptions, and upon the dates of ovulation in the months in which conception took place, are presented in Table I and in Fig. 1. The observations in Table I are arranged according to the day of conception, counting from the first day of the last menses.

The lengths of the cycles averaged from 24 to 35 days, inclusive. Conceptions (ovulation) occurred from cycle days 8 to 19, inclusive. Sixty per cent of the women conceived on cycle days 11 to 13, inclusive. The interval between ovulation and the first day of the next menstrual cycle ranged from 12 to 20 days, averaging 14.8 days.

*This investigation was aided by a grant from the Samuel S. Fels Fund.

Ovulation Day Determined by Rat Test
208 OVULATIONS IN 46 WOMEN WHO CONCEIVED

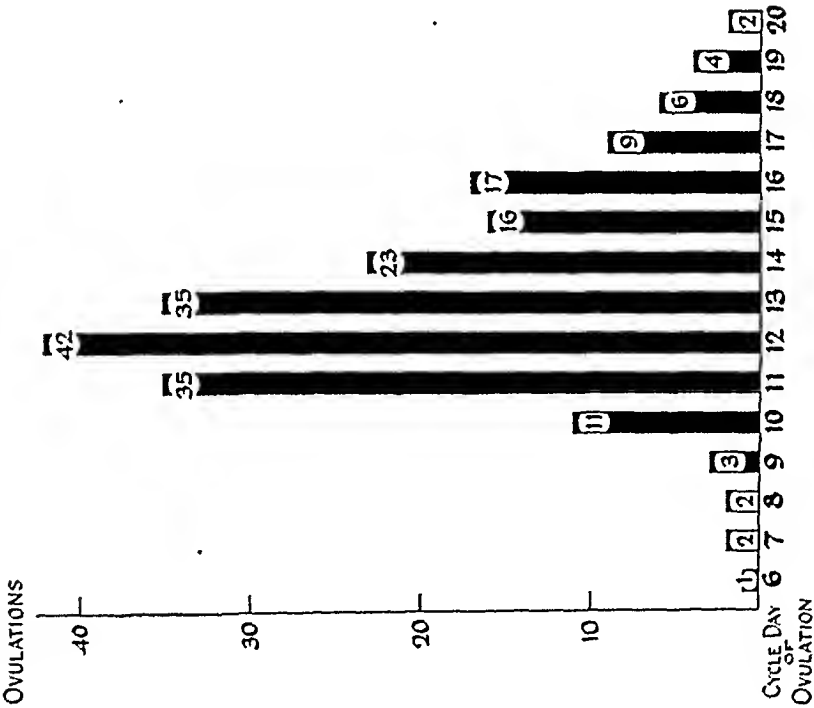


Fig. 2.

Fig. 2.—Each column represents the days of the cycle in which ovulations occurred. The length of each column and the number at its top indicate the number of ovulations which occurred on that cycle day. Ovulations occurred on cycle days 6 to 20, with the greatest number (42) taking place on cycle day 12.

Length of Menstrual Cycles
194 CYCLES IN 46 WOMEN PRIOR TO CONCEPTION

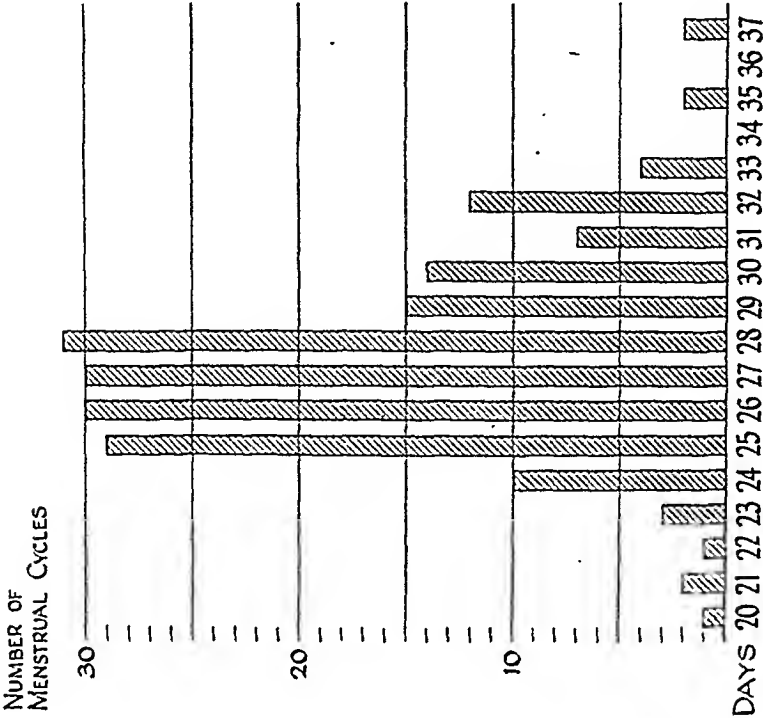


Fig. 3.

Fig. 3.—The base line (abscissa) records the length of the menstrual cycles in days. The ordinate represents the number of cycles studied. The majority of the cycles were 25 to 28 days in length, with a range of 20 to 37 days.

Seventeen of the conceptions followed insemination. Seven of these occurred on cycle day 11, 3 on cycle day 12, 2 on cycle day 13, 1 on cycle day 14, 2 on cycle day 16, and 2 on cycle day 19. The menstrual cycles of these 17 women averaged from 25.5 to 35 days in length. The postovulatory phases ranged from 12 to 17 days, averaging 12.8 days.

50 CONTROLLED CONCEPTIONS
WITH AVERAGE CYCLES 24-35 DAYS

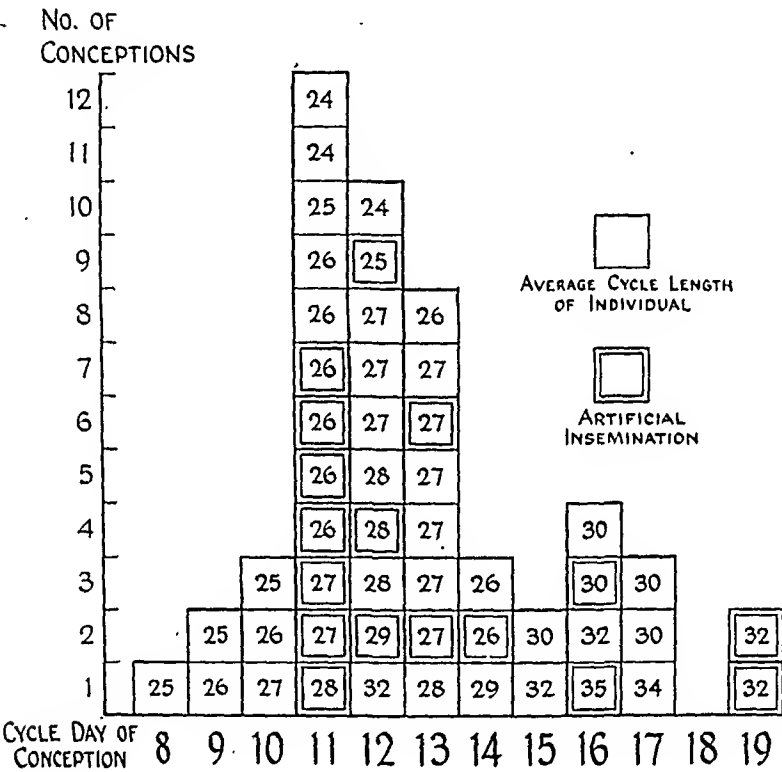


Fig. 1.—Each square represents a conception. The square is placed on the chart on the cycle day of conception. The number within the square is the length of the average menstrual cycle of that individual. The square within the square indicates that this conception resulted from insemination. Note that conceptions occurred most frequently on cycle day 11, next most frequently on cycle days 12 and 13. They ranged from the eighth to the nineteenth day of the cycle.

Table II shows the day of conception (ovulation) in relation to the length of the cycle. In general, the longer the cycle, the later was the day of conception (ovulation).

Fig. 2 shows graphically the day of ovulation in 208 cycles of the 46 women. These ranged from the sixth to the twentieth day. The largest number, 42, took place on cycle day 12; 35 occurred on cycle days 11 and 13. Fifty-four per cent of the ovulations, therefore, occurred on cycle days 11 to 13, inclusive.

Fig. 3 shows the lengths of 194 cycles which were studied during the months before the conceptions took place. These cycles ranged in length from 20 to 37 days, but with 62 per cent of them varying only from 25 to 28 days in length.

2. The fifty conceptions followed either insemination or intercourse practiced in relation to the predicted day of ovulation.

3. The conceptions (ovulations) occurred from cycle days 8 to 19, inclusive, with 60 per cent of them taking place on cycle days 11 to 13, inclusive.

4. The day of ovulation ranged from the sixth to the twentieth day of the cycle, with 54 per cent occurring on cycle days 11 to 13, inclusive.

5. The postovulatory phase averaged 14.8 days, with a range of 11.5 to 20 days.

It is with pleasure the author acknowledges the kindness of Dr. Douglas P. Murphy in making suggestions incorporated in this paper.

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TABLE II. THE DAY OF CONCEPTION IN RELATION TO THE MENSTRUAL CYCLE

| AVERAGE LENGTH OF MENSTRUAL CYCLE | CONCEPTIONS | DAY OF CONCEPTION | POST-OVULATORY INTERVAL RANGE |
|---|-------------|--|----------------------------------|
| DAYS | NUMBER | | DAYS |
| 24 | 3 | 11, 11, 12 | 12-13 |
| 25 | 5 | 8, 9, 10, 11, 12 | 13-17 |
| 26 | 11 | 9, 10, 11, 11, 11, 11, 11, 11, 11, 11, 13, 14, 14 | 12-17 |
| 27 | 12 | 10, 11, 11, 12, 12, 12, 13, 13, 13, 13, 13, 13 | 14-17 |
| 28 | 5 | 11, 12, 12, 12, 13 | 15-17 |
| 29 | 2 | 12, 14 | 15-17 |
| 30 | 5 | 15, 16, 16, 17, 17 | 13-15 |
| 31 | 0 | | |
| 32 | 5 | 12, 15, 16, 19, 19 | 13-20 |
| 33 | 0 | | |
| 34 | 1 | 17 | 17 |
| 35 | 1 | 16 | 19 |
| Range 24-35 | Total 50 | Range 8-19 | Total Range 12-20 |

Discussion

Hartman⁴ detected the ovulation time of the rhesus monkey by rectal palpation. He found that it occurred in this animal from the ninth to the eighteenth day, inclusive.

Corner, Hartman, and Bartelmez⁵ state that the ovulation day of the rhesus monkey ranges from the ninth to the seventeenth day, inclusive, of the cycle.

The author's observations upon the rhesus monkey ('46b) indicate that the ovulation of this animal ranges from day 8 to day 19 of the cycle.

Brewer and Jones⁶ determined the time of ovulation of 100 patients by microscopic examination of their corpora lutea. Their observations indicated that human ovulation occurs between the eighth and nineteenth days of the cycle.

The author studied the ovulation of 35 women prior to operation (unpublished data). Gross examination of the ovaries of these patients, and a microscopic study of the follicles and corpora lutea, revealed the fact that any ovulations which took place probably occurred on cycle days 9 to 18, inclusive.

The 50 conceptions of the 46 women reported here occurred on cycle days 8 to 19, inclusive.

In the cases in which ovulation was studied for several consecutive months in the same individual, 93 per cent of these women showed a variation in the time of occurrence of ovulation of less than 3 days, while 80 per cent exhibited a variation of less than 2 days. In comparison, 77 per cent of the series showed a variation in the length of their menstrual cycles of less than 3 days, while 65 per cent exhibited a variation of less than 2 days. Thus it appears that the time of ovulation is more constant than is the length of the menstrual cycle.

The interval between the day of ovulation and the first day of the next period ranged from 11.5 to 20 days, with an average of 14.8 days. In the monkey (Farris, '46b) this same interval varied from 9 to 17 days, averaging 13.6 days.

Summary

1. Two hundred eight ovulations were studied in forty-six women who experienced a total of fifty conceptions.

Technique

For the most part our patients received combined nembutal, demerol, and scopolamine analgesia in varying amounts before being anesthetized for delivery. Sixteen patients received no preliminary medication at all, and in this group no adverse effects were noted.

When satisfactory progress is being made, with primiparas we elect to anesthetize the patient with generous caput in sight and multiparas when near full dilatation. Under these conditions a spontaneous delivery with episiotomy can be expected, or at the most an elective outlet forceps. In this series the per cent of spontaneous deliveries might have been increased markedly, had the obstetrician chosen that course. If anesthesia is administered earlier than outlined above, the second stage is prolonged and/or a more difficult operative delivery may result. This is necessitated by virtue of the fact that the patient has no urge to "bear down" and bring the presenting part to a lower station.

When the patient is ready for anesthesia, the blood pressure and fetal heart are checked. She is placed in a sitting position on the side of the delivery table and supported by an assistant who stands in front of her. The patient's legs, flexed at the knees, hang over the edge of the table. She is instructed to place her arms over the assistant's shoulders and to bow her lumbar spine toward the anesthetist who works on the opposite side of the table. A generous area of the patient's back is scrubbed with soap and brush, rinsed with sterile water, and sprayed with merthiolate.

The third or fourth interspace is chosen, and a skin wheal is made with 1 per cent procaine solution to which is added 25 mg. of ephedrine sulfate, providing the blood pressure is not elevated. The second interspace may be used, since the level of insertion seems to have no effect on the eventual level of anesthesia. A number 22 gauge spinal needle is next introduced into the subarachnoid space, and 5 mg. of pontocaine dissolved in 1 c.c. of 10 per cent glucose is injected without withdrawal during the interval between contractions. In cases where speed is imperative, a number 20 needle may be used.

Following injection of the pontocaine, the patient is kept in the sitting position for forty-five seconds to permit the hyperbaric solution to descend. Next the patient is placed in the recumbent position with her head supported on a double pillow. The table is tilted to a 10 degree Fowler's position for fifteen minutes before leveling. The table may remain tilted 10 degrees during the entire delivery without inconvenience to the obstetrician or adverse effect on either the level or duration of anesthesia.

Relief from labor pains comes very rapidly, usually within one to two minutes after lying down. Complete pain insensibility is produced in five minutes. The anesthesia usually reaches a level just above the umbilicus, and lasts sixty to ninety minutes. After relief the blood pressure and fetal heart are rechecked and the patient made ready for delivery. In the average case a systolic and diastolic blood pressure fall of 5 to 10 mm. may be expected. Exceptionally, more of a drop may occur, and the delivery is delayed until a normal level results. If no anesthesia results, the procedure may be repeated. At least five minutes should be allowed prior to the second attempt. Care should be exercised that the medicated patient does not misinterpret the sense of touch for pain.

When one adheres closely to the above described routine, occasionally the heavy pontocaine does not reach a level high enough to anesthetize spinal nerves T10 and T11. In this situation perineal anesthesia is excellent, but the patient still has pain with contractions. Five minutes after the patient is placed in 10 degree Fowler position the level of anesthesia should be checked by pin prick.

VAGINAL DELIVERY UNDER HEAVY PONTOCAINE SPINAL ANESTHESIA*

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THE purpose of this paper is to present a review of 400 obstetric vaginal deliveries using heavy pontocaine anesthesia. The deliveries occurred during the period of Aug. 1, 1946, to Aug. 1, 1947, and were carried out at the U. S. Naval Hospital, Brooklyn, New York. The idea and procedure, with modifications, for using this type of anesthesia came from an article by Adriani and Roman-Vega¹ published in 1946, and another Parmley and Adriani.²

Selection of Cases

Over the period of time covered by our series there were 821 deliveries, thus we were not dealing with consecutive cases. The choice of anesthesia was in a great many cases left to the patient. The type of anesthesia was often determined by the physician on duty. It is the experience of about fifteen men, including interns under supervision, residents, and staff medical officers. Sometimes the rapidity of progress of a multiparous patient would frustrate any intention of spinal anesthesia. We preferred to deliver most of our more severe cardiac patients by continuous caudal anesthesia. Many breeches were excluded from the series because of preference for general anesthesia which seems to give better relaxation of the uterus.

Cases included were unselected in regard to age, parity, duration of labor, type of pelvis, and duration of gestation. There were 297 primiparas and 103 multiparas. We included the following:

- 13 pre-eclampsies
- 11 breeches
- 13 prolonged labors (over 30 hours)
- 7 prematures
- 4 myoma uteri
- 2 hypertensive disease
- 2 other cardiac disease
- 2 syphilis
- 6 ante-partum pyelitis
- 2 hydramnion
- 1 tuberculosis (pulmonary)
- 1 previous cesarean section
- 3 acute gonorrhea
- 2 elderly primipara (over 40 years)
- 1 placenta praevia
- 1 conglutinatio orificii externi

*The opinions expressed herein are those of the authors and not necessarily those of the Navy Department.

TABLE I. TYPE OF DELIVERY UNDER LOW SPINAL ANESTHESIA

| | NUMBER | PER CENT |
|---------------------------------|--------|----------|
| Spontaneous | 45 | 11 |
| Low forceps | 314 | } 89 |
| Mid forceps | 17 | |
| Seanzoni | 16 | |
| Breech (assisted or extraction) | 11 | |
| High forceps | 1 | |
| Total | 400 | 100 |

TABLE II. TOTAL NUMBER OF DELIVERIES

| | NUMBER | PER CENT |
|------------------|--------|----------|
| Spontaneous | 229 | 28 |
| Forceps | 581 | 70.7 |
| Cesarean section | 11 | 1.3 |
| Total | 821 | 100.0 |

TABLE III. INDICATIONS FOR FORCEPS

| | |
|---|-----|
| Elective | 275 |
| Prolonged second stage (over two hours without progress) | 38 |
| Transverse arrest | 10 |
| Posterior arrest | 24 |
| Toxemia | 1 |
| Fetal distress | 3 |
| Prolonged labor | 3 |
| Brow | 1 |
| Total | 355 |

eight long third stages are omitted, the average for the other 389 is 6.9 minutes. It is the policy at this hospital to allow the placenta to separate spontaneously and to gently express it with manual pressure. There were no Credé expressions.

Blood loss was estimated by at least a dozen different doctors, and the over-all average was just under 200 cubic centimeters. There were 13 cases where the estimated loss was over 500 c.c., and one case of over 1,500 cubic centimeters. The authors feel that there is no more danger from uterine atony than with other anesthesia, and that the blood loss is not appreciably altered. We do feel strongly, however, that labor is definitely slowed down, not only by the elimination of voluntary muscular effort, but also by reduction in both the frequency and force of the involuntary uterine contractions.

It may be pointed out that we had practically no cases of nausea and vomiting associated with the anesthetic.

Results

Of the 400 cases there were no maternal deaths. (There were no deaths for the total number of deliveries for the year.) Morbidity (temperature of 100.4° F. occurring on two or more days not including the day of delivery) was associated with 37, or 9.1 per cent, of the patients as illustrated in Table IV. There were no respiratory complications or meningitis cases. Of interest is the finding that of 13 patients who had prolonged labor of over thirty hours and who for the most part received prophylactic penicillin during labor, none were morbid.

Should the level not extend to the umbilicus the patient may be tipped to 15 to 20 degrees Trendelenburg for ten to fifteen seconds and then returned to the original position. This will invariably give the desired height of anesthesia.

One case will be cited to stress the importance of keeping in mind that the anesthesia is hyperparic. A doctor not too familiar with the technique tested his patient very soon after administering the pontocaine and, on finding his level too low, tipped her sharply into Trendelenburg for thirty to sixty seconds. The result was anesthesia to the point of respiratory depression which necessitated artificial respiration for a period of thirty minutes. After fifteen minutes the anesthesia will become fixed and there is little danger of such an accident. By the same token, if too much time is allowed to lapse, tilting will not cause any increase in the height of anesthesia.

Equipment

We have available several autoclaved spinal packs which include all the material necessary for administration of the anesthetic. A 25 mg. ampule of ephedrine sulfate, a 3 c.c. ampule of 10 per cent glucose, and a 10 mg. ampule of pontocaine snow are kept together in alcohol and are always ready for use. A stock solution of 1 per cent procaine is used for skin wheal anesthesia.

Two cubic centimeters of the 10 per cent glucose are withdrawn and injected into the 10 mg. of pontocaine snow. One cubic centimeter of this solution is employed. The total 25 mg. of ephedrine along with 2 to 3 c.c. of procaine is used.

Spinal Tray

- 2 single field cloths
- 4 gauze 4x4's
- 1 medicine glass
- 1 10 c.c. Luer-Lok syringe
- 1 2 c.c. syringe
- 1 #22 gauge 2" needle
- 1 hypo needle
- 1 #20 gauge spinal needle
- 1 #22 gauge spinal needle
- 1 ampule file

Failures

There were twenty cases classed as anesthetic failures. In this group we include those cases where spinal anesthesia was attempted and either no anesthesia resulted or insufficient anesthesia followed to eliminate the pain associated with contractions. Five of this group were subjected to a second attempt and in all cases the outcome was satisfactory. The other fifteen were delivered under another type of anesthesia or none at all was used. In a considerable number of cases—especially multiparas—we planned to use spinal but due to the rapidity of progress we resorted to general anesthesia. These were not classed as failures.

The total number of deliveries during this same period of time was 821 with the types recorded on Table II.

Indications for forceps in the spinal series are shown in Table III.

In 397 of the 400 cases accurate third stage time was recorded. The over-all average was 7.9 minutes. Four cases lasted over thirty minutes, and four lasted over sixty minutes. The longest third stage in the series was seventy minutes. There was one manual removal of the placenta. When the

cases, efforts to increase intracranial pressure will provide relief. After careful study we feel that the amount of spinal fluid lost (within average range) during the mechanics of lumbar puncture does not alter the incidence of headache. We were unable to determine any difference between using a No. 22 or No. 20 needle, although we feel that a smaller dural puncture may cause less difficulty. We believe that it is a hypotension headache and have found that an intractable case may be completely and immediately relieved by a small intrathecal infusion. This aspect will be dealt with more completely in another paper.

Condition of Infants

The fetal heart has been followed closely during all phases of the anesthesia, and no adverse effects have been noted. We feel that babies born under low spinal anesthesia suffer no ill-effects from the anesthetic agent. The infants have good color and muscular tone, and will cry and breathe spontaneously. Cases of asphyxia that occur can invariably be attributed to some other cause. There was an uncorrected fetal mortality of 0.75 per cent, or three deaths. Fetal abnormalities are included in Table VI.

TABLE VI. FETAL ABNORMALITIES

| CONDITION | NUMBER |
|--|--------|
| Prematurity (under 5½ pounds) | 7 |
| Pneumonia (died) | 1 |
| Asphyxia (requiring oxygen and artificial respiration) | 7 |
| Anencephaly (died) | 1 |
| Erythroblastosis (mild) | 1 |
| Congenital heart disease (died 2 weeks post partum) | 1 |

Summary and Conclusions

1. Four hundred cases of vaginal delivery using heavy pontocaine anesthesia have been reviewed.
2. The cases were unselected except for cardiacs and breeches.
3. The technique has been discussed fully. It is easy to perform and presents few pitfalls.
4. There were 5 per cent failures which can be attributed to faulty technique.
5. Labor is definitely slowed down, and a higher incidence of operative deliveries should be anticipated.
6. The third stage of labor is not altered, and blood loss is not enhanced by spinal anesthesia.
7. Nausea and vomiting are no problem.
8. There were no maternal deaths, and the fetal death rate was only 0.75 per cent. The anesthesia had no effect on the infant.
9. Morbidity with low spinal anesthesia presents no special problems. We had no pulmonary complications.
10. Spinal headache has been the most distressing and perplexing complications. If early ambulation were not employed, that would probably present no problem.

TABLE IV. MORBIDITY

| | NUMBER | PER CENT |
|---------------------------------|--------|----------|
| Puerperal infection | 17 | 4.2 |
| Urinary tract infection | 7 | 1.7 |
| Mastitis (three week follow-up) | 11 | 2.7 |
| Infection of episiotomy | 2 | 0.5 |
| Total | 37 | 9.1 |

Two patients had hemorrhages during the puerperium that warranted transfusion. One patient had difficulty knowing when she would void for six weeks after the baby was born. This complication subsided spontaneously. A peroneal paralysis with foot drop resulted in three patients. One patient seemed to be a definite pressure birth palsy with sensation and motor function restored in two months. Another patient sustained a peripheral stirrup nerve pressure injury that returned to normal in one week. In another case, a breech, no factor could be discovered to explain the paralysis. This patient was well in one month.

Catheterization was carried out every eight hours when necessary until a residual of less than 100 c.c. resulted. We found that 141, or 35 per cent of all patients, warranted catheterization at least once. Eighty patients had to be catheterized only once, 31 twice, 15 three times, and only 15 more than this. One patient had to be catheterized until the eighth postpartum day. We feel that the incidence of catheterization was not materially increased by the anesthetic agent. Over the period of time of this study, we have followed a regimen to early ambulation. Until the last three months of this series bathroom privileges were not allowed until the fourth day. During the last three months uncomplicated patients have been allowed bathroom privileges twenty-four hours post partum. The result has been that catheterization is rarely necessary.

Headache was one of the major difficulties. We included it as a complication when reference was made to it in the doctors' or nurses' notes. We made no attempt to select cases. All cases of headache have been included. Undoubtedly many were of origin other than from the spinal. We tried to eliminate the psychic factor by not revealing the type of anesthesia to the patient and by not suggesting the possibility of headache to her. We endeavored to make light of any headaches that occurred. For the most part aspirin and codeine provided relief. The over-all incidence was 19.5 per cent, or 78 cases. Discounting the mild two-day headaches, we are left with a 10 per cent incidence. The days of headache are as listed in Table V.

Typically, the onset is noted when the patient is first in the erect position after delivery. The patient complains first of a dull ache in the back of the neck that extends to the occipital region. In more severe cases the frontal area is involved. The headache disappears when the patient lies flat, and in milder

TABLE V. DAYS OF HEADACHE

| DAYS | NUMBER OF PATIENTS |
|------|--------------------|
| 1 | 21 |
| 2 | 17 |
| 3 | 12 |
| 4 | 16 |
| 5 | 8 |
| 6 | 2 |
| 7 | 3 |
| 8 | 2 |
| 9 | 0 |
| 10 | 2 |

VAGINAL CYTOLOGIC SURVEY IN GYNECOLOGIC CANCER

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CLOSE contact with the Tumor Board and gynecologic clinics of the White Memorial Hospital of the College of Medical Evangelists clearly impressed us with the large number of far-advanced genital cancers found in patients treated in this medical school clinic.

Examination of the literature and our own records revealed a favorable five-year survival in completely treated Stage I cancers of the cervix in 80 per cent of cases. In Stage II, cervical cancer, five-year survival is approximately 30 per cent; while in Stage III, only 10 to 15 per cent were alive in five years. Taking the over-all results from the leading American clinics, we find only 25 to 30 per cent of the women with arrested cervical cancer alive after five years. These facts forcefully manifested the need for early diagnosis.

Pack and Gallo¹ studied one thousand cases selected at random from the Memorial Hospital and the Patterson General Hospital from the standpoint of delay in treatment. The patient and/or physician was responsible for the delay in 35 per cent, and in only 20.7 per cent was there less than three months between onset of symptoms and the beginning of acceptable treatment. The patient was responsible for the delay in 44.3 per cent of the cases. The need for earlier diagnosis is imperative if present "cure" rates are to be improved upon by the use of our diagnostic and therapeutic facilities.

Vaginal cytologic methods, as reported by Papanicolaou and Traut,² seem to offer an additional method for early diagnosis and screening of a large number of patients. A study was made of the method in 1944, and, early in 1945, the authors spent some weeks in the laboratory of Dr. Papanicolaou.

Methods

On July 1, 1945, we began routine vaginal smears for all new admissions at the gynecology clinic in the out-patient department. By March 20, 1946, the first thousand satisfactory smears had been studied. Other smears from the offices of private physicians and from certain cancer detection clinics in the city are not included in this report, for the reason that adequate control and follow-up were not sufficiently complete to be significant in a statistical study.

The purposes of this vaginal smear survey were:

1. To test the sensitivity of the method in the detection of "cancer cells."
2. To determine if cancers might be discovered by this method which would otherwise be undetected.
3. To develop in the fourth-year student of medicine a "low threshold of suspicion" concerning cancer in the patients attended by him both in this teaching center and in later practice.

At no time did the vaginal smear method supplant adequate biopsy of endometrium, endocervix, cervix, or other portion of the genital tract. The

11. We feel that low spinal anesthesia is an easy and safe procedure, and should be part of the obstetric armamentarium.

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Addendum

Since this paper was submitted for publication, several hundred deliveries were carried out with 3.3 mg. of Pontocaine, according to the same technique. This amount of medication was found to be extremely safe, since the concentration produced excellent anesthesia but no loss of motor function. Thus, respiratory paralysis would be impossible.

CASE 1.—E. P., aged 41 years. A history of lower abdominal pain of six months' duration was given. Physical examination revealed a well-developed, well-nourished, colored woman forty-one years of age. Examination by assistants revealed no pathology except for an enlarged irregular mass in the lower abdomen, palpable bimanually and apparently continuous with the uterus. The diagnosis of uterine myoma was made and surgery advised. A routine vaginal smear was taken on the first visit.

At operation, the corpus was found to be of average size and to contain several myomas. Anterior to the corpus was a firm, friable mass, adherent to the bladder and to a four-inch length of the sigmoid colon. It grossly resembled a papillary adenocarcinoma of the ovary. This apparently was the tumor noted at the first clinical visit, and diagnosed as a myoma.

Biopsy of this tumor revealed a mucin-producing adenocarcinoma of the ovary which the pathologist suggested might be secondary to a carcinoma of the gastrointestinal tract. It was impossible to remove the tumor, and palliative deep x-ray therapy was recommended by the hospital Tumor Board.

Examination of the vaginal smear revealed numerous abnormal cells, most of which possessed an acidophilic cytoplasm with deeply stained and irregularly shaped large nuclei.

CASE 2.—D. S., aged 77 years. This patient was first seen in the clinic complaining of bloody spotting from the vagina for a year. On three occasions different gynecologists attempted endometrial biopsies, but were unable to enter the cervical canal and inadequate tissue was obtained.

Physical examination revealed an elderly, but well-preserved woman in her middle seventies. Pelvic examination demonstrated vaginal atrophy with obliteration of the fornices. The uterus was small and mobile, and there was no evidence of induration or fixation of a pelvic tumor. A vaginal smear revealed characteristic cancer cells.

Total hysterectomy was done because of the continual bleeding in spite of inadequate biopsies. The uterus was found to be largely destroyed by an endometrial cancer leaving a shell of myometrium containing the malignant growth. There was fear that tumor cells had been spilled into the abdomen at the time of operation, so postoperative x-ray was administered.

For two years the follow-up smears were negative, then became suspicious, and finally were definitely positive. Clinical evidence of recurrence was noted at this time, consisting of a friable mass in the vaginal vault.

CASE 3.—B. P., a sixty-nine-year-old white, obese woman entered the clinic with the complaint of low back pain of five years' duration and a mass in the lower abdomen first noticed six weeks ago.

Upon examination, masses were palpable in both lower quadrants, the right measuring 4 by 5 cm., and the left 8 by 14 cm. Pelvic examination suggested that there was a connection between the abdominal masses and the corpus uteri. A laparotomy was done, and a papillary cystadenocarcinoma of the ovary was found. The operation was followed by intensive post-operative radiation.

Five months after surgery, vaginal smears were made. Malignant cells with dark, irregularly outlined nuclei were found.

CASE 4.—V. K., aged 49 years, was a middle-aged woman who had ceased menstruation twelve years previously. Three months prior to examination she complained of a vaginal discharge, not bloody, but copious in amount.

Physical examination was essentially negative except for cervical erosion. A vaginal smear taken at that time revealed many large hyperchromatic nuclei appearing to be malignant. A curettage was done, and a squamous-cell carcinoma, grade III, was diagnosed from the curettings.

Surgery revealed an early carcinoma of the endocervix. The uterus was removed in toto.

cytologic studies were used merely as an adjunct. Clinical observation, biopsy, and section of tissue removed at surgery were used as a check on the accuracy of the smear method of cancer detection. The slides from each individual case were sent to the laboratory in a separate bottle containing a fixative and accompanied by a card on which the date, name, and referring clinic, date of last menses, recent endocrine therapy, and radiation therapy, were recorded. These cards were given a serial number and used as a cross file. Each patient had on her data card suitable space for a description of the cytologic data. Particular attention was given to the amount of cornification, the presence of basal cells, leucocytes, erythrocytes, monocytes, and, of course, cells suggestive of malignancy.

The material for the smear was obtained by aspirating the vaginal fornices with a pipette and rubber bulb. The material was expressed on to a micro slide, and a second slide was laid gently on the pool of fluid to spread it evenly. By pulling the slides apart lengthwise, two smears of quite even thickness were obtained. These were immediately immersed in a mixture of equal parts of 95 per cent ethyl alcohol and ether for fixation. (Later we have used 95 per cent ethyl alcohol alone, and more recently, isopropanol with equally good results.)

More recently the vaginal fluid has been obtained on the posterior blade of a dry bivalve speculum, further simplifying the procedure. The house staff and externs now routinely examine with a dry speculum before making the digital examination. If history or findings suggest the possibility of a new growth, the accumulation of vaginal fluid including a portion obtained by direct friction against the cervix is used for the smear.

Occasionally the physician will allow the smear to dry before fixation. Such slides show much less clarity of detail in the individual cell examined than those in which fixation is immediate. Staining is done by the method of Papanicolaou with minor variations as determined by results.

Results

Of the first one thousand consecutive gynecologic patients, nine hundred fifty-eight had negative smears. Of these, four had previously received radiation for known uterine cancer. Cancer cells disappear from the smears after adequate radiation therapy in the majority of cases. In forty-two cases, the smears were positive or suspicious. Of these forty-two cases, twenty-five had carcinoma, as proved on biopsy. Four vulvar, fifteen cervical, five endometrial, and one site-unstated, carcinomas were detected.

Of the forty-two "positive" cases, seventeen had no carcinoma, but were diagnosed on biopsy as papilloma of the cervix, functional bleeding, cervicitis, leukoplakia, and uterine myoma. In twelve of the seventeen without carcinoma, no biopsy was made, but the cases on repeated examination were clinically negative.

There were nine hundred seventy-one cases that had no cancer detectable clinically and/or by biopsy. Of these, nine hundred fifty-six had negative smears, or an accuracy of 98.6 per cent. Of the twenty-five untreated carcinomas, none were missed. These, added to the treated cases, make twenty-nine cases or an incidence of 2.9 per cent of carcinoma in this routine smear survey. We do know, however, of two cases, later than this series, in which carcinoma of the fundus was missed on the smear.

Several cases were encountered in the series in which the smear led to the diagnosis in the absence of definite clinical evidence. A brief résumé of these cases follows.

CASE 5.—M. W., a seventy-seven-year-old woman, came to the clinic because of a burning sensation in the vagina and burning on urination. The vulva was described as being covered by a "curdlike" exudate on the labia minora and vaginal mucosa. A smear at this time was suspicious for cancer.

Three months later a smear was positive. Shortly after this smear, a biopsy revealed intraepithelial squamous carcinoma of the vulva, and wide local excision was advised. Following smears were negative.

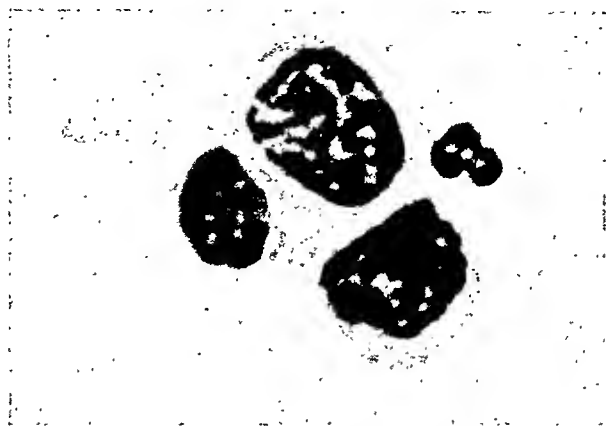


Fig. 3.—Direct impression smear from patient with tissue diagnosis of squamous carcinoma of vulva. Not mentioned in text.

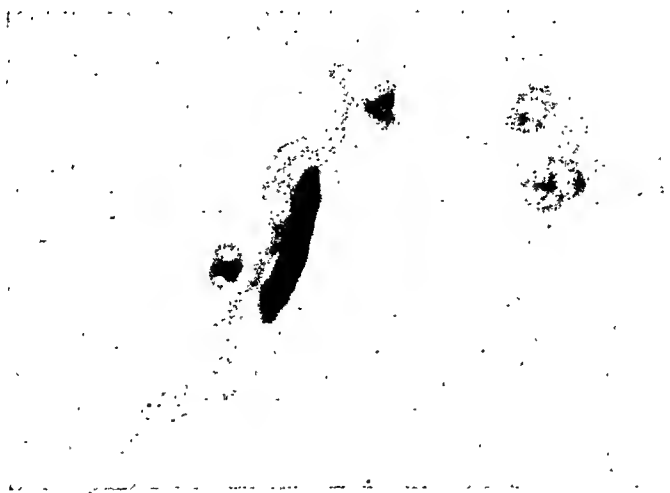


Fig. 4.—Vaginal smear from patient with tissue diagnosis of cancer of the cervix. Not mentioned in text.

Conclusions

We would conclude that vaginal cytologic studies are:

1. A reasonably accurate cancer exclusion method.
2. A less accurate diagnostic test.
3. A method of cancer detection leading to diagnosis in certain cases where clinical evidence is lacking.

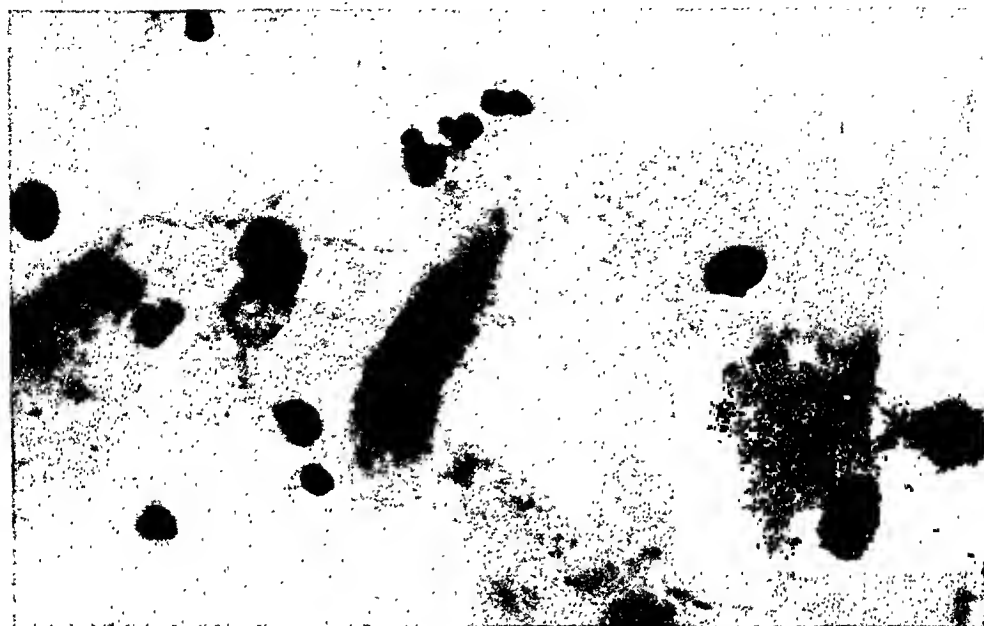


Fig. 1.—From Case 1. Abnormal epithelial cells found in the vaginal smear with tissue diagnosis of ovarian carcinoma.



Fig. 2.—Vaginal smear from patient with tissue diagnosis of endometrial carcinoma. Not mentioned in text.

SHOCK FROM POSTERIOR PITUITARY EXTRACT

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THERE is very little question that a form of shock may be produced, in particularly sensitive or sensitized individuals, by the injection of a solution of posterior pituitary extract. The occurrence of shock within a short time after injection of such a solution and the ability to reproduce the shock picture with the injection of a minute portion of the material into the same patient was demonstrated by McMann.¹ Because the fear of shock constantly haunts the obstetrician, many of us have discarded the use of the ordinary solutions of posterior pituitary extract and have taken up the routine use of ergot preparations or the deproteinized posterior pituitary extracts. In obstetric practice, the use of these products serve as more than adequate replacements for the posterior pituitary extracts. Unfortunately, these products do not act as efficiently in gynecologic practice, their action being negligible on the nonpregnant uterus. We have proved this latter point to our full satisfaction by injecting uteri under direct vision through laparotomy incision, and have observed the action of the various drugs on the uterus.

For many years, posterior pituitary extract has been used as an aid to the control of excessive bleeding during the course of gynecologic surgery. Official cognizance of this procedure was not made until 1932, when Heaney² published the technique of its use. Since that time it has become a routine part of the gynecologic surgeon's armamentarium, as evidenced by notes in Curtis' textbook³ and in papers such as that of Danforth.⁴

In using posterior pituitary extract locally in gynecologic surgery, an occasional patient will develop shock, ostensibly as the result of the use of the extract. Many more patients will show more or less minor reaction with moderate fall in blood pressure and circumoral pallor which will revert to normal spontaneously or after the application of simple methods of combating these conditions.

During the past several years we have collected five cases of shock which we feel had been produced by posterior pituitary extract. Several days after the patients' recovery from the initial shock, they were tested by injecting one minim of various products intradermally. The size of the area of erythema and the blood pressure were checked at five-minute intervals. Five products were used for testing in each individual, two separate posterior pituitary extracts, one deproteinized posterior pituitary extract and two ergonovine preparations. Tables I and II are self explanatory.

We wish to acknowledge the liberal grants from the American Cancer Society and the Cancer Prevention Clinic of Los Angeles which made this work possible.

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condition can return to normal. The use of parenteral adrenalin chloride or ephedrine sulfate (except where cyclopropane anesthesia is being used) plus the use of intravenous infusions of fluids, blood plasma or whole blood tend to restore the patient in short order. Since death has resulted from this type of shock, one must always bear in mind the possibility of such an occurrence, and the means to combat such shock must always be on hand in the operating room when posterior pituitary extract is used.

We have recently changed to the routine use of a deproteinized posterior pituitary extract in our surgical work, but the ideal of local hemostasis is far from achieved. Thus, in an attempt to safeguard the patient, we are practically defeating our purpose in using a product that does not produce adequate hemostasis equal to that which can be obtained with the unpurified product. We have encountered only five cases of shock in the thousands of obstetric and gynecologic patients cared for at the Presbyterian and Mount Sinai Hospitals. This is a very small percentage, and in analyzing shock we must take into account other factors, evaluate them, and then place the blame on the posterior pituitary extract only when other possible causes have been ruled out.

After reviewing all the evidence, we must conclude that a posterior pituitary extract is always potentially dangerous in a sensitized or sensitive individual. This might prove serious in an allergically sensitive patient or in one with an unstable or damaged cardiovascular system. So, to be absolutely certain, we should confine our use of obstetric oxytocics to the nonbiologic types (ergot derivatives). Since these substances are of little or no value on a nonpregnant uterus, and since in certain types of vaginal surgery hemostasis is necessary to allow for perfect visibility and blood conservation, we must seek an oxytocic drug for uterine contraction and local vasoconstriction. In dealing with a large fibroid uterus which we are approaching abdominally, an injection of posterior pituitary extract directly into the uterus will decrease the size of the tumor rapidly. By this process a sizable and valuable amount of blood is pressed into the general circulation from the tumor, providing a good method of autotransfusion. Therefore, since the deproteinized product lacks the efficiency desired, we must resort to the use of ordinary posterior pituitary extract in cases where extra blood, decrease in size of tumor, and increase in facility of approach are of value. Such a product can be used with relative safety if the patient is non-allergic, has a stable and undamaged cardiovascular system, and when the operating room is equipped for the combat of shock if evidence of this complication presents.

Conclusions

1. "Pituitary shock" occurs as the result of the direct pressor action of posterior pituitary extracts upon the coronary arteries.
2. This shock is readily combated by the use of adrenalin chloride or ephedrine sulfate, and intravenous infusions of fluids, whole blood, or blood plasma.
3. For safe obstetric use, posterior pituitary extracts may be replaced by the ergot derivatives.

TABLE I. DIAMETER OF SKIN REACTIONS IN CENTIMETERS

| PRODUCT USED* | 5 MINUTES AFTER INJECTIONS | | | | 10 MINUTES AFTER INJECTIONS | | | | 15 MINUTES AFTER INJECTIONS | | | | 1 HOUR AFTER INJECTIONS | | | |
|---------------|----------------------------|---------|---------|------|-----------------------------|---------|---------|------|-----------------------------|---------|---------|------|-------------------------|---------|---------|------|
| | PIT. #1 | PIT. #2 | PIT. #3 | ERG. | PIT. #1 | PIT. #2 | PIT. #3 | ERG. | PIT. #1 | PIT. #2 | PIT. #3 | ERG. | PIT. #1 | PIT. #2 | PIT. #3 | ERG. |
| Patient #1 | 3 | 3 | 7 | 1 | 4 | 4.5 | 8.5 | 1 | 4.5 | 5 | 10 | 1 | 2 | 1.5 | 2 | 1 |
| Patient #2 | 3 | 4 | 3.5 | 1 | 3.5 | 5 | 4.5 | 1 | 4 | 6 | 5 | 1 | 1 | 1.5 | 1 | 1 |
| Patient #3 | 2 | 3 | 2 | 1 | 3 | 3.5 | 3 | 1 | 3.5 | 4.5 | 4 | 1 | 1 | 2 | 1 | 1 |
| Patient #4 | 3 | 3.5 | 3 | 1 | 4 | 4.7 | 3.8 | 1 | 4.5 | 6.5 | 5.2 | 1 | 1 | 2 | 1 | 1 |
| Patient #5 | 2.5 | 3 | 4 | 1 | 5 | 6 | 5.5 | 1 | 6.5 | 7.8 | 6.5 | 1 | 1 | 1 | 1 | 1 |

*Pit. #1—Posterior pituitary extract.

Pit. #2—Posterior pituitary extract.

Pit. #3—Deproteinized posterior pituitary extract.

Erg.—Ergonovine.

TABLE II. BLOOD PRESSURE CHANGES

| TIME | BEFORE INJECTION | 5 MINUTES AFTER INJECTION | | | | 15 MINUTES AFTER INJECTION | | | | 1 HOUR AFTER INJECTION | | | |
|------------|------------------|---------------------------|---------|---------|------|----------------------------|---------|---------|------|------------------------|---------|---------|------|
| | | PIT. #1 | PIT. #2 | PIT. #3 | ERG. | PIT. #1 | PIT. #2 | PIT. #3 | ERG. | PIT. #1 | PIT. #2 | PIT. #3 | ERG. |
| Patient #1 | 110 | 100 | 100 | 110 | 110 | 90 | 70 | 100 | 110 | 90 | 100 | 120 | 110 |
| | 70 | 50 | 60 | 70 | 70 | 40 | 40 | 70 | 70 | 50 | 60 | 80 | 70 |
| Patient #2 | 100 | 84 | 80 | 100 | 100 | 76 | 70 | 90 | 100 | 90 | 98 | 98 | 100 |
| | 64 | 50 | 40 | 60 | 64 | 40 | 40 | 50 | 64 | 50 | 60 | 60 | 64 |
| Patient #3 | 120 | 100 | 98 | 110 | 120 | 90 | 84 | 90 | 120 | 104 | 100 | 108 | 120 |
| | 70 | 60 | 54 | 68 | 70 | 50 | 48 | 50 | 70 | 64 | 56 | 60 | 70 |
| Patient #4 | 114 | 90 | 88 | 94 | 114 | 80 | 76 | 82 | 114 | 100 | 98 | 108 | 114 |
| | 70 | 60 | 54 | 50 | 70 | 50 | 40 | 48 | 70 | 60 | 62 | 68 | 70 |
| Patient #5 | 128 | 100 | 98 | 106 | 128 | 88 | 90 | 94 | 128 | 94 | 114 | 120 | 128 |
| | 80 | 50 | 62 | 70 | 80 | 40 | 52 | 60 | 80 | 70 | 68 | 70 | 80 |

Comment

According to pharmacologists and anesthesiologists, so-called "pituitrin shock" is a phenomenon produced by the pressor substances present in the extract used. This pressor action is specifically acting on the coronary arteries, producing vasoconstriction and, subsequently, shock. Pendleton, Ball and Rhode⁵ subscribe to this theory, as do Adelman and Lennon,⁶ stating that the specific action of the pressor substances on the coronary arteries results in "myocardial anoxia, cardiac dilatation, and decreased cardiac output." Simon and Ryder,⁷ on the other hand, hold that the entire process of reaction to posterior pituitary extract is a foreign protein reaction due to the presence of the protein in the extract. Our studies would tend to favor the first theory since in the patients we tested the greatest reactions were obtained in testing with a deproteinized agent.

Within a few minutes after the injection of the extract, the blood pressure begins to drop rapidly and alarmingly. Along with this, there is a marked increase in the pulse rate with the pulsations at the temples and the wrist becoming imperceptible, while the patient develops a marked pallor. Unless treatment is instituted quickly, the patient goes into deep shock rather rapidly. These patients respond to treatment very well, and before the operation is completed, the

ARSENICAL ENCEPHALOPATHY IN PREGNANCY WITH RECOVERY

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Encephalopathy has always been regarded as a grave complication of arsphenamine administration. Wilson¹ gives the mortality rate as approximately 75 per cent. In a series of 155 cases reviewed by Glaser, Imerman and Imerman,² 120 patients died. Many investigators (Klaften,³ Ingraham,⁴ Paley and Pleshette,⁵ Cormia,⁶ Moore⁷) believe that this complication arises more frequently when arsenicals are used during pregnancy. Moreover, recovery is then less common. Kühnel,⁸ in 1935, listed 23 fatalities and since then Plass and Woods⁹ and Ingraham⁴ have further reviewed the literature. We were able to find only 5 instances^{8,10-13} of recovery, none from American sources. In Table I, the essential features of these cases are summarized. All had received neoarsphenamine, and symptoms usually appeared after the second dose. Severe headache was a constant complaint. Although coma was present in one case and a convulsion reported in another, all had a relatively mild form of the disease.

TABLE I. REPORTED CASES OF RECOVERY FROM ARSENICAL ENCEPHALOPATHY IN PREGNANCY

| NAME OF AUTHOR | YEAR | MONTH OF PREG-NANCY | HEAD-ACHE | NEUROLOGIC SIGNS | RESIDUAL DEFECT | OUTCOME OF PREGNANCY |
|--|------|---------------------|-----------|---|--|---------------------------|
| LÜCKEN ¹⁰ | 1920 | 5 | + | HYPERREFLEXIA DYSARTHRIA | NONE | NORMAL CHILD |
| REIF ¹¹ | 1921 | 4 | + | COMA CONJUGATE DEVI- ATION OF EYES INCONTINENCE BILATERAL BABINSKI | NONE | NOT STATED |
| KÜHNEL ⁸ | 1933 | 8 | + | APATHY BABINSKI | NONE | NORMAL CHILD |
| SPILLMAN, WEILLE AND WEISSMANN ¹² | 1936 | 5 | + | HEMIPLEGIA APHASIA INCONTINENCE | HEMIPARESIS | NORMAL CHILD |
| NELSON, MCGIBBON AND GLYN-HUGHES ¹³ | 1943 | 5 | + | CONVULSION (HISTORY) STUPOR | NONE | NORMAL CHILD |
| KANTOR AND LEVIN | 1948 | 6 | + | STUPOR HEMIPARESIS DYSARTHRIA NYSTAGMUS | HEMIPARESIS PSEUDOBUL- BAR PALSY | ECLAMPSIA NORMAL CHILD |

With the use of British Anti-Lewisite (BAL), the prognosis of this complication has changed. Reporting on this treatment of arsenic poisoning, Eagle and Magnuson¹⁴ include 55 patients with encephalitis of whom 12 died, a mortality rate of 22 per cent. In a personal communication, Eagle stated it was not recorded if any of these patients were pregnant. The dosage of BAL recommended by these authors is presented in Table II.

4. For use in gynecologic surgery, there is no adequate substitute for posterior pituitary extract.

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slow and tremulous. The other neurologic details were unchanged. On October 21, the spinal fluid pressure was 30 mm. of water, and the protein content had fallen to 48 mg. per 100 c.c.

The following day, information was received concerning the injections given for the verrucae acuminata. These consisted of 0.3 Gm. of neosarsphenamine on October 9 and 12, with headache starting 9 hours after the second injection. It was now clear that we were dealing with an encephalopathic reaction to neosarsphenamine. Although ten days had already elapsed, specific treatment with BAL was instituted. On a basis of 2.5 mg. per kilogram of body weight, 160 mg. (1.6 c.c.) were given intramuscularly every 4 hours for 48 hours, 3 times a day for 2 days and twice a day for 8 days, a total of 5,440 mg. (54.4 c.c.). After the first 3 doses, she seemed definitely improved. The speech was more distinct and no longer tremulous. Nystagmus was less definite. The right hand seemed stronger but the right lower extremity was still weak. The left plantar response was occasionally flexor, the right remaining extensor. On October 28, the right toes were appreciably stronger and weak abdominal reflexes could be elicited on that side.

Liver function tests gave clear evidence of diffuse hepatocellular damage. The cephalin flocculation reaction was four plus in 48 hours. Hippuric acid excretion (Quick's method) was 0.98 Gm. Bromsulfalein was retained (15 per cent) at 1 hour. The serum proteins were normal in their total content but the ratio was reversed (albumin 3.6, globulin 4.4). The icterus index was 7 and blood urea nitrogen content 6 mg. per 100 c.c. The prothrombin time was 97 per cent of normal. She was placed on a high carbohydrate diet to which choline (2 grams, 3 times daily) and brewer's yeast were added.

Rather late during the treatment, reports of two cultures of spinal fluid became available. From fluid obtained October 19, a mildly hemolytic *Staphylococcus aureus* was grown only in the broth, and the specimen on the 21st yielded a nonhemolytic *Staph. aureus*, again only in broth. In the absence of clinical or cytologic evidence of bacterial meningitis, we considered these organisms contaminants.

On October 29, several of the larger warts were removed with electrocautery but further excision was deferred until after the termination of pregnancy. On October 30 the patient received another transfusion of 500 c.c. of whole blood. The following day she developed an acute pyelitis, due to *Escherichia coli* and *Proteus vulgaris*, which subsided in four days.

Neurologic examination at the time of discharge on November 7 revealed a mild right hemiparesis, greatest in the foot. Although not yet completely normal, her speech was easily understood. The ocular movements were normal. All muscular reflexes, including jaw jerk, were increased, with bilateral Hoffmann and Babinski signs, stronger on the right.

Her physician sent us a report on Jan. 16, 1947. She continued to improve after leaving the hospital. On December 23, a trace of albumin was noted in the urine with "everything else within normal limits." Four days later, she developed eclampsia and had repeated generalized tonic and clonic convulsions. Labor was induced and she was delivered spontaneously within twenty-four hours of a premature living male child weighing 5½ pounds. Resuscitation of the infant was difficult. The postpartum course was uneventful.

The patient returned to us on Aug. 7, 1947. She stated that there was definite improvement in walking and speech during the first two months following delivery. However, she still dragged the right foot. The speech remained a little slurred, and at times she choked in drinking. There was difficulty in control of laughter, which was always appropriate, but often led to crying.

Neurologic examination showed a mild right hemiparesis with weakness of the hand and foot. The right lower face was weak on volitional innervation but showed exaggerated movement in smiling. All the deep reflexes were increased, more so on the right, with a brisk jaw jerk. Hoffmann and Babinski signs were present bilaterally, stronger on the right. A feeble abdominal reflex was elicited on the right side only.

TABLE II. THE ADMINISTRATION OF BAL AS RECOMMENDED BY EAGLE AND MAGNUSON.¹⁴

| ARSENICAL ENCEPHALOPATHY | DOSE OF BAL | INJECTIONS PER DAY | NUMBER OF DAYS |
|-----------------------------|-----------------|-----------------------|----------------------|
| Mild cases | | | |
| Initial | 2.5 mg. per kg. | 4 | 2 |
| Follow-up | 2.5 mg. per kg. | 1-2 | until recovery |
| Severe cases: | | | |
| Initial | 3 mg. per kg. | 6 | 2 |
| Follow-up | 3 mg. per kg. | 2 | 10 or until recovery |

The following case is reported for three reasons: 1. It demonstrates the outcome of a pregnancy complicated by encephalopathy due to neoarsphenamine. 2. Recovery from this complication is uncommon. 3. BAL was used with safety during pregnancy.

Case Report

D. K., hospital number W41237, an 18-year-old white primigravida, was admitted to Parkland Hospital on Oct. 18, 1946, in the twenty-sixth week, having received prenatal care in her home town. With the exception of vaginal and perineal warts, for which some injections were given, her course was uneventful until the onset of her present illness. The past and family histories were essentially negative; convulsions had never occurred.

On October 12, she complained of headache and sore throat. Two days later she developed mild lethargy and a nonproductive cough. The next day there was difficulty in swallowing and she vomited several times. Her husband noted twitching of the mouth and slurring of speech, so that it became increasingly difficult to understand her. She had no fever or rash. On October 16, she was admitted to another hospital where lumbar puncture was performed. The cerebrospinal fluid was under "normal pressure" and contained no cells. The Kahn test was negative on both spinal fluid and blood. There was a trace of albumin in the urine and the white blood count was 12,200 per c.mm. Penicillin and intravenous glucose were given. On the following day, she developed weakness of the right arm and leg, which increased during the afternoon. Poliomyelitis was suspected and she was transferred late that evening to Parkland Hospital.

She arrived in a semistuporous condition. Her speech was slow and poorly articulated. The fundi and pupils were normal. External rotation of the eyes was slightly limited, with fine vertical nystagmus on upward gaze and horizontal nystagmus on lateral, both being well sustained. There was right hemiparesis, most marked in the lower extremity. The right arm showed flexor spasticity. The palate and tongue moved fairly well. Active corneal reflexes and a lively jaw jerk were elicited. The deep reflexes were all exaggerated. Strong Hoffmann and Babinski signs were present bilaterally, with unsustained ankle and patellar clonus. The abdominal reflexes were absent. Position sense and perception of pain were intact. There was no stiffness of the neck or Kernig sign.

The uterus was enlarged to the size of a twenty-five week pregnancy with fetal heart tones heard in the left lower quadrant, rate 130 per minute. Verrucae acuminata were noted in the vagina and on the vulva and cervix. The remainder of the physical examination was negative except for evidence of dehydration. The blood pressure was 120/76. The temperature was 99.6°F. on admission and fell to normal within four hours.

The cerebrospinal fluid was clear and colorless, under a pressure of 130 mm. of water, with a negative Queckenstedt test. It contained 8 cells per c.mm. and 87 mg. of protein per 100 c.c. There was a mild anemia with a normal leucocyte count. A three plus acetone reaction was found in an otherwise normal urine. Blood chemistry studies revealed normal values and the Kline reaction was negative.

With a tentative diagnosis of multiple sclerosis complicating pregnancy, a vasodilator regimen was started, consisting of histamine by slow intravenous infusion and nicotinic acid by mouth. A transfusion of 500 c.c. of citrated blood was given. On October 20, she was more alert and her speech was slightly more forceful although it was still indistinct,

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An electroencephalogram showed cerebral dysrhythmia, greater on the left. The alpha rhythm was dominant, symmetrical and well modulated, with a rate of 11.5 cycles per second. Slow waves, varying from 4 to 6 cycles per second, occurred throughout but were larger and more numerous in all areas of the left cerebral hemisphere. Hyperventilation produced a moderate buildup with bursts of large 6 per second waves in both frontal regions at 50 seconds. These findings are consistent with the clinical picture of bilateral cerebral disease more pronounced on the left side.

Pelvic examination showed the uterus well involuted. The verrucae had completely regressed. The vagina, cervix and adnexa were normal.

Comment

It must be conceded that the favorable outcome of this case cannot be attributed unconditionally to the specific therapy. Ten days had elapsed before BAL was started and it is clear that the encephalopathy was relatively mild. The prognosis was accordingly more favorable. Some improvement had already occurred when the correct diagnosis became evident. However, lessening of the neurologic disability began immediately after the institution of BAL therapy. Had BAL been administered earlier, it is probable that recovery would have been more complete. The total dosage which our patient received was considered adequate.

The outcome of the pregnancy deserves comment. Clason¹⁵ suggested a possible relationship between eclampsia and arsenical poisoning, comparing the encephalopathies of these conditions. Perhaps the residual encephalopathy furnished the basis for conversion of a nonconvulsive toxemia into eclampsia. Rosenbaum and Maltby¹⁶ reported a high incidence of cerebral dysrhythmia in women previously eclamptic. It is of importance to note that, in spite of the cerebral and liver damage from neoarsphenamine and the administration of large doses of BAL, the pregnancy was not interrupted and a healthy infant was born.

Finally, the case warrants a note of caution against the indiscriminate use of arsphenamines. These are potentially dangerous drugs and should be administered only with the utmost care to avoid serious reactions.

Summary

An 18-year-old primigravida received two injections of neoarsphenamine for verrucae acuminata. Shortly after the second injection she developed symptoms of arsenical encephalopathy. She exhibited improvement with British Anti-Lewisite, although it was not administered until ten days after the onset. The pregnancy was not affected by this complication during the period of observation at Parkland Hospital, but she developed eclampsia prior to delivery. Examination seven months postpartum showed a residual neurologic defect and cerebral dysrhythmia. BAL probably had no deleterious effect on the pregnancy.

We should like to express our gratitude to Dr. William F. Mengert for his valuable suggestions.

TABLE I. INDICATIONS FOR CESAREAN SECTION

| PRIMIPARAS | |
|--|----|
| Fetomaternal disproportion | 19 |
| Elderly primiparity—35 yrs. 2; 36 yrs. 3; 38 yrs. 1; 39 yrs. 2; 41 yrs. 2 | 10 |
| Prolonged labor; no progress—22-79 hrs. | 10 |
| Severe pre-eclampsia | 3 |
| Abruptio placentae | 2 |
| Double vagina, cervix, and uterus | 1 |
| Double vagina and cervix | 1 |
| Uterus duplex and septate vagina | 1 |
| Prolapse of the cord (baby lived) | 1 |
| Marginal placenta previa, partial separation, 6 hr. labor without progress | 1 |
| Two previous spontaneous abortions | 1 |
| Spontaneous rupture of membranes with no labor after 12 hrs. | 1 |
| MULTIPARAS | |
| Repeat section | 8 |
| Previous stillborn breech; large baby (9 lbs. 10 oz) | 1 |
| Essential hypertension; large baby (8 lbs. 11 oz.); disproportion | 1 |

Our cesarean section incidence of 13.7 per cent compares very favorably with Tompkin's⁴ report of 211 cases of breech being handled by 17 "certified" obstetricians, where the cesarean section incidence was 14.2 per cent. Potter, Erving, and Brown,² reporting on 786 cases, which, like ours, were delivered in a general hospital, showed an incidence of only 10.8 per cent abdominal deliveries.

Cesarean section, like all other abdominal surgery, seems to have undergone a decrease in risk during the past ten years, and, though still showing a high morbidity rate, as will be pointed out later, is having its indications extended somewhat. This certainly applies to breech, where the ability to diagnose fetomaternal disproportion is limited by the inaccessibility of the head. Elderly primiparity, and failure to go into labor after spontaneous rupture of the membranes are also important factors in deciding to deliver abdominally.

Actually, statistics on cesarean section are more valuable if the maternal morbidity and mortality rates and the fetal mortality rate are compared with the same as shown in vaginal deliveries. The results in our cases follow.

Puerperal Mortality and Morbidity.—In our entire series, no mother died.

The morbidity rate was obtained according to the standard set by the Maternal Welfare Committee, of a temperature of 100.4° or more on any two days exclusive of the first 24 hours, and has been analyzed in Table II for the various types of delivery.

TABLE II. PUERPERAL MORBIDITY

| | |
|------------------------------------|---------------|
| All cases | 12.6 per cent |
| All vaginal deliveries | 9.9 per cent |
| Prolonged labor (vaginal delivery) | 18.0 per cent |
| Cesarean section | 29.5 per cent |

Thus we see that abdominal delivery produces three times the morbidity rate that vaginal delivery does. It should be mentioned that, with few exceptions, those patients having postpartum fever were only mildly ill and completely recovered in three to five days.

The author,⁵ in a previous report on 133 cases of breech delivered at Touro Infirmary during 1933 to 1937, found the over-all morbidity rate to be 18.7 per cent.

Fetal Mortality and Morbidity.—As with maternal morbidity, fetal mortality varies with the type of labor and delivery, and an analysis is presented in

BREECH PRESENTATION AND DELIVERY*

A Review of 445 Consecutive Cases in a General Hospital

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THIS report is presented for the purpose of reviewing the statistics on breech presentation and delivery for the ten-year period, Jan. 1, 1937, to Jan. 1, 1947, in a general hospital, and to review some of the recent literature on the subject.

The cases included in this study are single pregnancies only, seven months or more, where presentation as well as delivery was breech.

Incidence.—During the ten-year period mentioned, there occurred in Touro Infirmary a total of 13,577 deliveries, of which 445, 3.1 per cent, were breech, conforming to the above-mentioned standard. In 14,000 cases at the Chicago Maternity Center, the incidence was 3.24 per cent; at Chicago Lying-in, 4.2 per cent among 35,000 cases,¹ while Potter, Erving, and Brown report 3.2 per cent in 23,916 cases.²

Among our cases, there were 261 primiparas and 184 multiparas.

Duration of Labor.—The average length of labor, where delivery occurred per vagina, was 17 hours, 37 minutes in primiparas, and 11 hours, 34 minutes in multiparas. The type of delivery varied, some being spontaneous, some spontaneous with breech assistance, and still others by decomposition of a frank breech and extraction after full dilatation of the cervix.

Irving and Goethals have long advocated breech extraction as soon as full dilatation of the cervix has occurred, and Vogt, Bryant, and McConnell,³ following this technique, report on 177 single breech cases after the period of viability. The average duration of the first and second stages of labor of their primiparas is 15 hours, 43 minutes, while in multiparas it is 11 hours, 24 minutes. Apparently there is some saving of time to a primipara, but not to a multipara.

Designating twenty-four hours as the upper limit of normal labor, it was found that prolonged labor occurred in 42 primiparas (16 per cent) and 19 multiparas (10 per cent). It is generally conceded that the breech is inferior to the head as a dilating wedge.

Methods of Delivery.—Vaginal delivery occurred in 384 patients (86.3 per cent), 212 of whom were primiparas, and 173 multiparas.

There were 61 cesarean sections (13.7 per cent), 19.3 per cent of deliveries in primiparas and 5.4 per cent in multiparas. Of the ten sections performed upon the latter, eight were repeat sections. Table I reveals the indications for cesarean sections in our group.

*Read at a meeting of the New Orleans Gynecological and Obstetrical Society, December, 1947.

Breech presentation is very frequent up until the 34th to 36th week of pregnancy, when spontaneous version usually occurs. Vartan¹³ says that one patient in four has a breech at some time during pregnancy, and it is very frequently found at the 30th week. Parity seems to play little part, and spontaneous version occurs in three out of five cases, most frequently complete by the 32nd week and accomplished, as a rule, by a single movement.

One of the most important causes of persistent breech seems to be extension of the legs, rendering spontaneous as well as external version much more difficult and unlikely. Tompkins¹² has also added that the degree of fetal activity is directly proportional to the possibility of spontaneous version.

External version has many strong advocates, and it is reasonable to assume that, if a vertex presentation can be safely obtained, and the baby have a three to five times greater chance of surviving, the operation is well worth attempting. Providing that a few general rules are followed, external version can be done safely, and the incidence of successes increases with incidence of attempts. Vartan¹³ was successful in 67.0 per cent in 330 cases, and Ryder⁸ reports an even higher rate. In the consecutive deliveries of 1,700 women receiving good prenatal care, there existed 258 breech presentations at some time during pregnancy. In his attempts at external version, he was completely successful in 92.5 per cent, truly an excellent record. External version was followed by reversion in 2.8 per cent, and complete failure to perform even one external version occurred in only 4.7 per cent. Ryder points out that failure in external version is due either to extension of the legs or to delaying attempts until too late in pregnancy. He experienced no failures, whether the legs were extended or not, if done prior to the eighth month. He also suggests that in attempting external version, the patient should lie on her back, relaxed both physically and mentally, the bladder should be empty, the finger tips should be used for gentle manipulation, the fetal heart tones should be checked frequently, the breech should be pushed up, and turning should be done so that flexion of the baby's body occurs simultaneously. However, if failure should occur, the opposite direction may be tried. Trubkowitz and Arehangel'sky¹¹ have attempted to dispel any existent fear as concerns complications attending external version. They were successful in 90.5 per cent of their attempts on 324 cases. The usually feared complications, they comment upon thus:

1. Premature labor:
Is frequent with breech presentation.
Only 1.0 per cent followed external version.
2. Bleeding:
Occurred only once in their series, and had no effect on pregnancy or labor.
3. Premature separation of the placenta:
Was not encountered.
4. Premature loss of liquor amnii:
Occurred in 2.0 per cent of cases. Certainly is not significant.
5. Prolapse of the cord:
0.4 per cent in head presentation
2.1 per cent in breech presentation
0.4 per cent in breech presentation after successful external version
11.5 per cent in breech presentation after unsuccessful external version.
6. Twisted cord:
16.8 per cent among all cases
5.2 per cent after successful external version

Table III. To obtain corrected fetal mortality, the following were omitted from the gross mortality statistics:

1. All babies weighing less than 2500 Gm. (5½ pounds).
This is the standard set for "prematurity."⁶
2. All macerated stillbirths.
3. All antepartum deaths.
4. All monsters.
5. One baby who died postoperatively, due to a congenital anomaly of the small bowel.

TABLE III. FETAL MORTALITY

| | GROSS MORTALITY (PER CENT) | CORRECTED MORTALITY (PER CENT) |
|------------------------------------|-------------------------------|-----------------------------------|
| All cases | 13.0 | 4.7 |
| All vaginal deliveries | 13.8 | 4.9 |
| Prolonged labor (vaginal delivery) | 24.5 | 6.5 |
| Cesarean section | 8.9 | 3.5 |

Among those babies surviving, there were:

- 1 Brachial plexus injury,
- 2 Fractures of the humerus,
- 1 Fracture of the clavicle,
- 1 Fracture of the tibia and fibula.

In my previous series of 133 cases,⁵ the corrected fetal mortality was 5.2 per cent. We have, therefore, reduced our maternal morbidity rate 33 per cent during the past ten years, and our fetal mortality rate 10.0 per cent. It should be mentioned that the cesarean section incidence during 1933 to 1937 was only 4.5 per cent as compared to 13.7 per cent shown in this series.

Table IV reveals the corrected fetal mortality as reported during the past few years by different authors.

TABLE IV. CORRECTED FETAL MORTALITY IN BREECH DELIVERY

| YEAR | AUTHOR | NO. OF CASES | CORRECTED FETAL MORTALITY (PER CENT) |
|------|--|-----------------|---|
| 1943 | Tompkins ⁴ (17 "certified" obstetricians) | 211 | 2.7 |
| 1944 | City of Moscow ¹¹ | 3148 | 10.1 |
| 1945 | Potter, Erving, and Brown ² | 786 | 9.6 |
| 1945 | Vogt, Bryant, and McConnell ³ (breech extraction as soon as cervix was fully dilated) | 177 | 4.4 |
| 1946 | Guyer and Heaton ⁷ | 708 | 4.5 |

Ryder⁸ has stated that the fetal mortality in breech delivery is five times that in vertex. No report on breech would be complete without giving credit to Holland,⁹ who, in 1922 in his classic presentation, stated that tears of the tentorium cerebelli and cerebral hemorrhage are almost always present in dead breech fetuses, and that the fetal mortality rate is rarely less than 8 to 10 per cent.

Review of the Recent Literature

The cause of breech presentation has always been a matter of speculation. Most textbooks list prematurity, placenta previa, hydrocephalus, multiparity, multiple pregnancy, contracted pelvis, and pelvic tumors as "classical" causes, but, as pointed out by Tompkins,¹² only about one-sixth of the cases of breech can be accounted for by the above-mentioned factors.

tures of long bones may be avoided by exerting pressure only over the flexor surface at an articulation, and rupture of an abdominal viscus avoided by bearing in mind the ill effects of undue abdominal compression.

8. The delivery of the baby should never be hurried, since the most frequent cause of fetal death, intraeranian injury, is the usual result of such injudiciousness.
9. The use of elective cesarean section is indicated when, after careful internal pelvic examination, evaluation of the size of the baby, and possibly x-ray, doubt exists as to a successful delivery per vaginam, regardless of the age of the patient.

Summary

1. A consecutive series of 445 breech deliveries occurring over a ten-year period in a general hospital is reported.
2. Delivery occurred per vaginam in 86.3 per cent, and by cesarean section in 13.7 per cent.
3. The over-all maternal morbidity rate was 12.6 per cent.
4. No maternal deaths occurred.
5. The gross fetal mortality was 13.0 per cent, and the corrected mortality, 4.7 per cent.
6. A review of the recent literature on breech is presented.
7. Suggestions are made for the successful handling of cases of breech presentation.

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Certainly then, it is apparent that the low incidence of complications is more than offset by the increased safety to the baby delivered as a vertex.

Insofar as the method of delivery in a persistent breech is concerned, there have long been two schools of thought: first, those conducting labor the same as with a vertex, and only assisting after spontaneous delivery of the breech and body, in extracting the shoulders and head; and second, those who feel that it is advantageous to do a breech extraction on all cases as soon as the cervix is fully dilated and retracted. The latter method has been popularized by Irving and Goethals at the Boston Lying-in, who first recommended it in 1926. Vogt, Bryant, and McConnell,³ using this technique on 177 patients, report a corrected fetal mortality rate of 4.43 per cent. In our own series, the corrected fetal mortality rate for all vaginal deliveries of breech was 4.9 per cent, and for the most part our cases were handled conservatively, manual aid being given only after the breech and body had been delivered spontaneously. This method has been recommended by DeLee and Greenhill.¹

The incidence of cesarean section has increased, since there are certain very definite indications for this operation, and though it still shows a rather high morbidity and mortality rate, its safety has increased along with abdominal surgery in general. Grieg¹⁰ warns that the risk is still five times greater than in vaginal delivery. Because of the inadequacy of pelvoencephalography in breech, many borderline cases of fetomaternal disproportion are now being sectioned. Rupture of the membranes with an unprepared lower uterine segment and failure to go into labor within twenty-four hours constitute another indication, according to Grieg. Among the 211 cases of breech handled by 17 "certified" obstetricians, the cesarean section rate was 14.2 per cent and their corrected fetal mortality rate, 2.7 per cent. (No data was given concerning the mothers.) Potter, Erving, and Brown² performed 85 cesarean sections (10.8 per cent) in 786 cases of breech with no fetal loss. Their maternal morbidity rate for all types of delivery was 11.5 per cent. In our series, the cesarean section rate was 13.7 per cent, our over-all maternal morbidity rate, 12.6 per cent, and we lost 3.5 per cent of the cesarean section babies.

Recommendations for the Successful Handling of Breech Presentation

1. Careful repeated examinations of patients during the prenatal period, so that breech can be determined early.
2. Attempt at external version should be made about four to six weeks prior to term, observing the general rules previously mentioned.
3. Despite their relative infrequency, such factors as pelvic contractions, multiple pregnancy, monstrosities, and obstructing tumors should be ruled out by x-ray.
4. During labor, exhaustion and dehydration should be prevented by the adequate use of sedatives and fluids, either orally or parenterally.
5. Watchful waiting during labor, with frequent checking of the fetal heart tones. At the first or second pelvic examination, careful checking for an occult prolapse of the cord should be made, and after rupture of the membranes, it should be determined if a true prolapse exists.
6. Encourage and coach the mother to make full use of her expulsive forces after the second stage begins. In the event that a foot or knee presents at the vulva, and extraction is contemplated, first determine if the cervix is completely dilated, since extremity presentation may occur prior to the end of the first stage.
7. Adequate inhalation anesthesia, a liberal episiotomy, and the Potter technique, with or without Piper forceps, depending upon the need, all constitute important contributions toward a successful delivery. Frac-

left iliac fossa, small parts to the right and the breech engaged. The fetal heart was best heard at the umbilicus. A roentgenogram of the abdomen showed a full breech presentation with arms at the sides and cervical spine in extreme hyperextension. The occiput rested on



Fig. 1.—(Official U. S. Navy photograph.) Appearance of the abdomen at the thirty-seventh week of gestation.

the lumbar spine (Fig. 1). There was no roentgenographic evidence of fetal anomaly. Five days later, the patient was hospitalized and roentgenograms in anteroposterior and lateral projections were made. No change was noted. At the thirty-eighth week of gestation, an

BREECH PRESENTATION WITH HYPEREXTENSION OF THE NECK AND INTRAUTERINE DISLOCATION OF CERVICAL VERTEBRAE*

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WITH the exception of Stein's^{1,2} work on deflection attitudes in breech presentation and references to his work,³ there is little in the literature to signify that extension of the cervical region of the spinal column can and does occur in breech presentation. Stein emphasized the value of roentgenographic study, and it is interesting to note that the diagnosis in practically all reported cases of deflection attitudes has been made only after roentgenologic examination. Rösslin⁴ in the sixteenth century mentioned extreme deflection attitudes and advised delivery by manual traction on the presenting part. However, his sketches are highly imaginative and his discussion theoretical, so that it is impossible to determine his true understanding of the problem.

Falls,⁵ in 1917, described an unusual fetal position. The baby lay somewhat obliquely with the head in the left iliac fossa, the lumbar region of the spinal column markedly hyperextended and the knees presented in the lower uterine segment. He applied the apt term "opisthotonus fetus." In the last two weeks of pregnancy, he made several unsuccessful attempts at external version. With the onset of spontaneous labor, the membranes ruptured. The fetal heart tones suddenly became poor at three fingerbreadths of cervical dilatation and breech extraction was promptly performed. The baby was born in asphyxia pallida and failed to respond to measures of resuscitation. Permission for necropsy was refused. Careful examination of the body revealed no apparent abnormalities.

Burns,⁶ Knowlton,⁷ and Kobak⁸ have since reported cases of deflection attitudes in transverse presentations. Knowlton called this fetal position "flying foetus," a term which graphically describes it. These authors effected delivery by cesarean section and live babies resulted. Kobak's patient underwent section during labor after 7 cm. of cervical dilatation had occurred. The baby required resuscitation.

The following unique case of breech presentation with hyperextension of the neck and intrauterine dislocation of cervical vertebrae is reported.

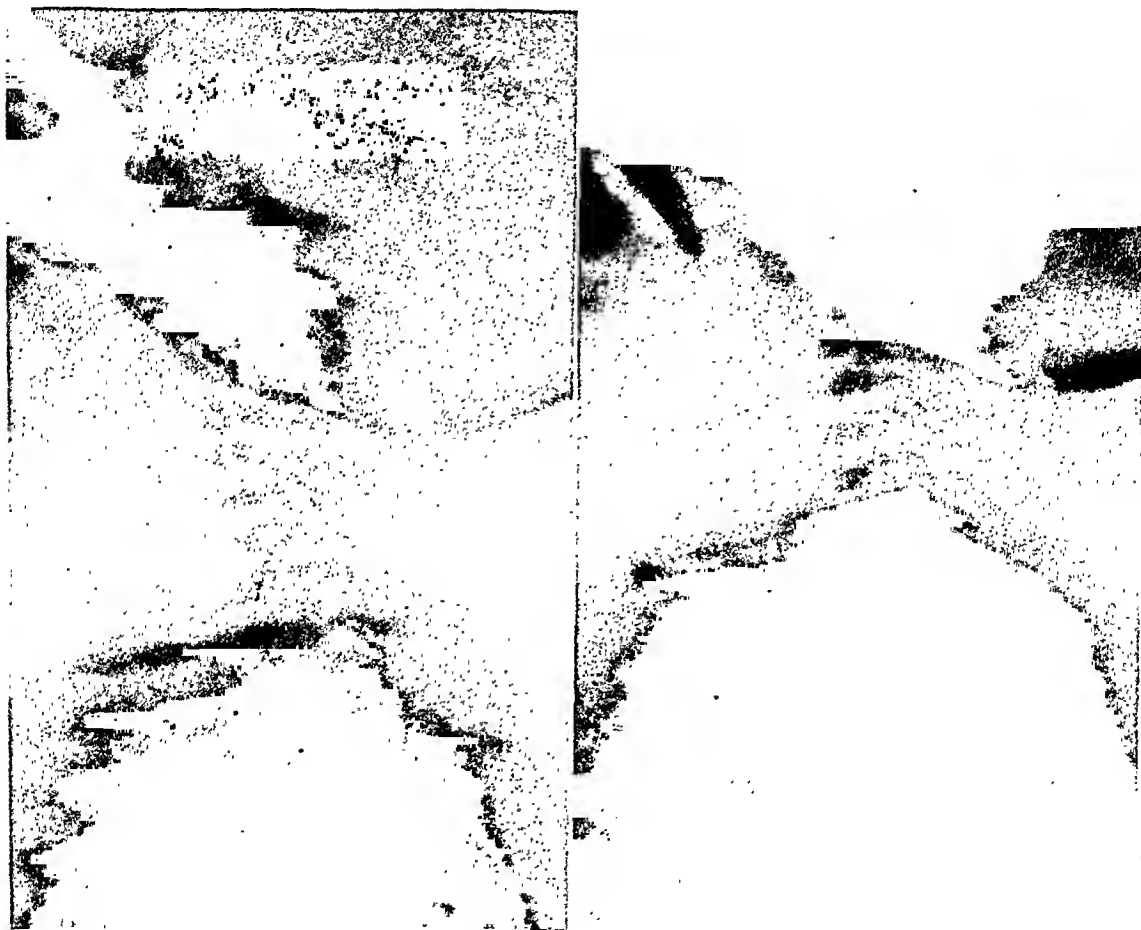
Report of Case

A thirty-six-year-old secundigravida, primipara, presented herself for prenatal care Feb. 21, 1946, and gave as the date of her last menstrual period Oct. 25, 1945. Her history revealed that she had had a normal pregnancy in 1930, which terminated in spontaneous delivery of a boy weighing seven pounds, six and a half ounces (3,353 Gm.) after a total of two and one-half hours of labor. In 1934, appendectomy and suspension of the uterus had been performed. The patient's general health had been good and her menstrual history was normal. General physical examination revealed a large woman with a justo major pelvis. The uterus was enlarged to the size of that of a sixteen weeks' gestation and was in normal position. The blood was Rh positive and Kahn reaction was negative. Repeated urinalysis gave negative results. The prenatal course was subjectively uneventful. Quickening occurred Feb. 24, 1946.

At the thirty-fourth week of gestation, abdominal palpation revealed the vertex floating at the inlet. At the thirty-seventh week of gestation, examination revealed the vertex in the

*The patient whose case is reported received her medical care at U. S. Naval Hospital, Jacksonville, Fla., while the author was on active duty as Lieutenant Commander in the U. S. Navy.

Stein⁹ has had a somewhat similar breech presentation that occurred in an arcuate uterus. Delivery was by cesarean section. No cervical dislocation was noted. Inquiries addressed to several other obstetricians of wide experience¹⁰ failed to elicit knowledge of a similar case, and views as to proper management were divergent. Titus and his Pittsburgh group endorsed the selection of cesarean section as the method of choice for delivery. Bartholomew and Reid suggested vaginal delivery. Version was not seriously considered because it seemed impossible to dislodge the breech from the pelvis without further extending the fetal neck. The same reason seemed to countermand a trial of labor since transection of



A.

B.

Figs. 3A and B.—Cervical spine of a normal eight-day-old baby. Slightly varying lateral projections were made to try to demonstrate any technical error or artefact that might be interpreted as dislocation of a vertebra.

the cervical cord appeared entirely possible. Since no case has been reported in which a physician has knowingly delivered an infant vaginally from such a position, it is not possible to predict the outcome. Falls's case would seem the closest analogy reported.

It is well known that complete necropsy reveals a high incidence of cerebral hemorrhage as the principal cause of stillbirth and neonatal death. That damage to the spinal column and cord is frequently associated with breech delivery and especially with version and extraction has been pointed out by Spencer,¹¹ Stolzenberger,¹² Sachs¹³ and Ehrenfest.^{14, 15} Excepting Spencer, these authors have pointed out that hyperextension of the cervical spine in the execution of the Mauriceau maneuver is particularly dangerous, and more so if any lateral traction be made at the time hyperextension exists. Zellweger¹⁶ has recently reported four cases of spinal cord damage in infants, in one of which there was marked forward

elective, low cervical, cesarean section was performed with the patient under spinal anesthesia. There were several pea-sized subserous uterine myomata. The suspension had apparently been of the Gilliam type but no distortion of the uterus that could not be ascribed to the fetal position was demonstrable. No adhesions were noted. A boy weighing seven pounds, one and one-half ounces (3,213 Gm.) was easily delivered and the baby cried spontaneously.

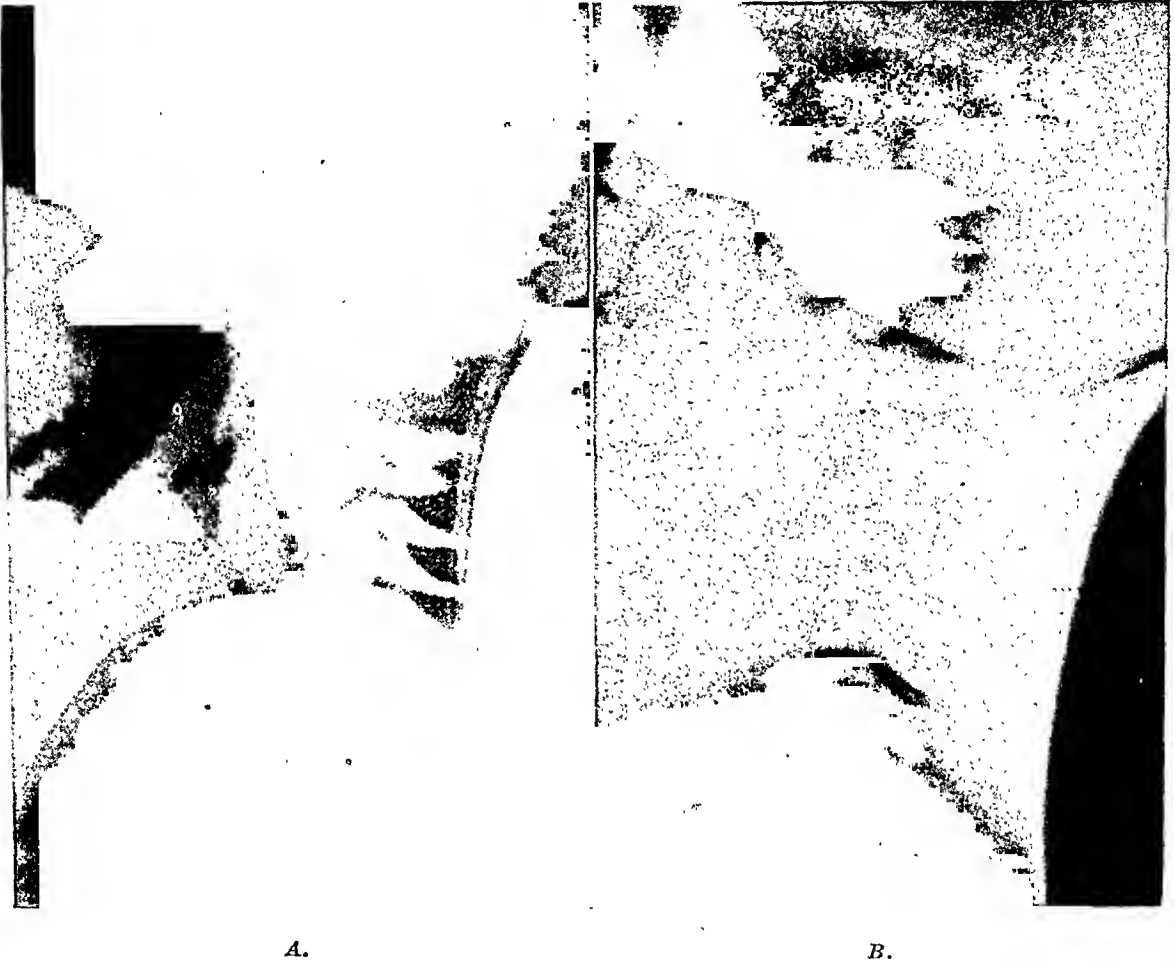


Fig. 2.—(Official U. S. Navy photographs.) A. Appearance of the cervical spine on the sixth day of extrauterine life. Note forward dislocation of C I, II and III on C IV. B. Appearance on the eighteenth day of life.

The mother's postoperative course was uneventful. The baby had a good cry, moved all of his extremities, and nursed well. The neck seemed longer than average and was quite flaccid. Neurologic examination gave negative results. Roentgenographic examination of the cervical spine on the sixth day after delivery revealed forward dislocation of the first, second, and third cervical vertebrae on the fourth (Fig. 2A). The baby was kept in Trendelenburg position and immobilization of the head and neck was attempted by means of sandbags. On the eighteenth day of life roentgenograms again revealed the dislocation (Fig. 2B). The baby was then referred to Dr. F. L. Fort of Jacksonville, Florida, who applied a light metal splint to immobilize the head and neck. A roentgenogram made when the baby was four months of age revealed reduction of the dislocation. At five months, the baby held his head up well and was normal on physical examination. Owing to the rarity of dislocations of the cervical spine in newborn infants, roentgenograms were made of the cervical spine of a normal eight-day-old baby. Slightly varying lateral projections were made and these served to confirm the actual dislocation noted in the case presented (Fig. 3A and B).

NORMAL PREGNANCY FOLLOWING TUBOUTERINE IMPLANTATION

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THERE is a very extensive literature on various operative procedures for sterilization and subsequent pregnancies following such procedures. Some such pregnancies were normal uterine pregnancies with normal deliveries and others were extrauterine. We refer primarily to operations performed for the purpose of sterilization. But, unfortunately, many surgeons are in the habit of removing tubes indiscriminately, when the tubes need either no surgery or some minor plastic procedure, such as opening a closed fimbriated end or excising some constricting fibrous bands. While modern pelvic surgery in honest, capable hands leans toward preservation, it would appear that the ovary is the main beneficiary in this change of attitude, which has come about only too slowly. And even here, many surgeons are only too prone to remove an ovary which needs either no surgery or only the puncture or removal of some cysts, or, at most, only a partial resection, since half an ovary is better than no ovary, and a woman can become pregnant with half an ovary and one tube (even a poor and distorted tube). We believe the matter of depriving a woman in the child-bearing age of motherhood is one that has not been given enough serious thought. The uterus itself is only too often removed by surgeons who are either unscrupulous or ignorant of uterine pathology. This is not a subject for discussion here.

We have compiled a list of 125 references relative to the operative procedures of establishing fecundity following operations for sterilization and allied subjects. These references are in Spanish, French, German and English. We have most of the articles in foreign languages either translated verbatim or abstracted, and we have read most of these articles, but believe it will serve no useful purpose to list them all with this article. They cannot all be referred to here, and anyone interested in this subject is familiar with the vast literature on sterilization and methods to correct this condition. Anyone not interested would not appreciate the amount of study involved and would not use the references. We shall merely list the references quoted here, and attempt to give some idea of the infrequency of pregnancy following such corrective surgery.

As above stated, pregnancy has followed sterilization operations in many cases. It has also, in many instances, followed surgery not performed for the purpose of sterilization but which was, by its very nature, sterilizing in character, such as bilateral salpingectomy and/or oophorectomy and hysterectomy. Here an operative procedure to correct sterilization is most called for, but, in our case, the patient was sterilized "on purpose" in a State Institution. The details will be given later.

dislocation of the sixth on the seventh cervical vertebra with consequent transection of the cervical cord at this level. Breech delivery had been effected with much traction but there is no mention made as to the use of the Mauriceau maneuver. Tovernd¹⁷ found central nervous system hemorrhage in 38.8 per cent of 953 newborn infants coming to necropsy. He put great emphasis on the occurrence of abnormal pregnancy as the principal cause of hemorrhage but it is noteworthy that of the infants exhibiting hemorrhage into the central nervous system, more than 25 per cent was born by breech delivery.

It is hoped that the report of this case and the review of the pertinent literature will serve to render the obstetrician more conscious of deflection attitudes in breech presentation and more mindful of the vulnerability of the cervical spine and cord. Roentgenography is paramount as an aid in diagnosis and should be used much more often in breech presentations that persist until labor supervenes. Even in the absence of other positive evidence, it would seem reasonable to suppose that labor in the presence of hyperextension of the cervical spine could cause fatal damage to the cord.

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cavity by means of a long probe. The abdomen was opened and the fibrosed areas where section and ligation had been performed were excised. These areas were adjacent to the uterus.

The tubes were then about 1 inch shorter than normal. The uterus was then incised transversely across the fundus from cornu to cornu where the interstitial portions of the tubes would normally be. The whole length of the incision was carried into the uterine cavity. One strand of the silkworm gut was threaded through one tube, leaving about 1 inch projecting through the fimbrial end and the other strand of gut was similarly threaded through the other tube. The uterine ends of the tubes were split for about $\frac{1}{4}$ inch and each tube, one lip only, was sutured to the uterus at the site which insured the tubes were lying in their normal position. The uterus was then closed. The two strands of silkworm gut were withdrawn on the eighth day. Insufflation of the tubes later showed them to be patent, and hysterosalpingography confirmed this finding.

There have been many similar types of technique described with subsequent pregnancies, some of which have gone to full term. However, the number of full term pregnancies has been comparatively small.

An ever-present danger following tubouterine implantation is tubal pregnancy. Sovak⁷ describes such a case. Sovak had a large experience in plastic operative procedures to establish fertility following chronic pelvic disease and sterilization operations. Many of his cases were occluded oviducts following chronic pelvic disease. This case was operated upon in February, 1932, and both tubes were found to be occluded. By his special technique, a bilateral tubouterine implantation was performed. Seventeen months later, the patient had a uterine pregnancy followed by abortion. In August, 1935, she was again hospitalized and operated upon for tubal pregnancy. Both tubes appeared normal except for the right tubal pregnancy. There was no apparent contracture at the tubouterine juncture. Insufflation later showed the left tube to be patent. This case is of interest because it permitted a survey of the end results of tubouterine implantation. One of the essential complications of tubouterine implantations is contracture due to cicatrization of the newly created ostia in the horns of the uterus upon the implanted tubes. This complication would naturally prevent pregnancy completely, but it is generally agreed that the cause or main cause of tubal pregnancy is the pathologic damage in the occluded tubes following pelvic disease. And since many plastic operations to establish fertility are on diseased tubes, it naturally follows that the incidence of tubal pregnancy following such plastic operation in these cases will result in a high rate of tubal pregnancies.

This hazard is not imminent in tubouterine implantation to establish fertility after sterilization operations on essentially normal tubes.

In plastic surgery for reconstruction of the oviducts occluded at the fimbriated ends the procedure is relatively simple. In these cases a phimosi operation is done at the ends of the tubes, leaving them patent at the end of the operation. The chances of pregnancy following this procedure, in spite of the high incidence of tubal patencies is very meager. Some such cases can be opened by insufflation pressure. Holden⁸ reports a case of full-term pregnancy following a phimosi operation on the occluded fimbriated ends of the tubes. Rubin, in discussing Holden's paper, states he has done many tubouterine implantations and has never had a pregnancy follow. Peightal, also, in discussing Holden's paper, states that in three years on his Gynecological Division of the Roosevelt Hospital fifteen cases of tubouterine implantation were done and no pregnancies followed, although 80 per cent of these cases resulted in tubal patencies.

In any discussion of female infertility, the status of the husband must also be considered. This should include a morphologic sperm count. The general health of both husband and wife must be considered.

Douglass¹ reports an operative technique to correct sterility following bilateral salpingectomy. He reports four cases. The ovary is mobilized, and transposed to the cornu of the same side, providing the infundibulopelvic ligament is long enough, and sutured into a wedge-shaped defect made in the cornu, in which the short intrauterine tube still remains, and is placed against the open distal end of the tube. Peritonealization is done over this area. Pregnancy did not follow three of these cases, but one was admitted to the hospital five and one-half months after surgery for uterine bleeding of one week's duration. She was curetted and the pathologic report was typical placental tissue with infection. Hence impregnation did occur, even though it did not go to term. Douglass concludes such surgery is worth while, and believes it should be encouraged.

Martin,² Dudley,³ and Storer⁴ described special operations of ovarian transplant following bilateral salpingectomy but their cases, although some pregnancies followed, all terminated in abortion. The reader is referred to their original articles for their technique.

The series of cases reported by Estes⁵ included four pregnancies, two of which went to full term. Twenty-two women in this series had shown fertility before contracting pelvic disease which made bilateral salpingectomy necessary. His operation is a periuterine transposition, leaving a certain amount of the uterine portion of the tube in situ and fixing a portion of the corresponding ovary on its pedicle directly over it.

In general, attempts to establish fertility following bilateral salpingectomy have met with almost universal failure with only few exceptions. The literature is rich in material but poor in results.

Extrauterine pregnancy has been reported following supravaginal hysterectomy but only with surgical interference, to end in failure. It would serve no purpose to list all the references in the literature concerned with this problem. Also, attempts at impregnation after bilateral oophorectomy, by grafts of homogenous ovarian tissue have failed. In the few such cases reported, following bilateral oophorectomy, with homogenous ovarian tissue grafts, it is assumed pregnancy followed as a result of ovulation with accessory ovarian tissue rather than activity or ovulation of the homogenous graft. These grafts (homogenous) absorb or become scar tissue the same as autogenous free grafts or transplants of ovarian tissue which is placed in the uterine cavity or cornu of the uterus, while the ovary is deprived of its pedicle with a free and adequate blood supply. The above discussion has to do mainly with pregnancy following bilateral salpingectomy or bilateral oophorectomy or both, after attempts to establish fertility by surgical means. It is true pregnancy has followed bilateral salpingectomy but these pregnancies have been extrauterine and have been terminated by surgical interference to remove the fetus before term.

In a very broad sense, a general statement can be made that attempts to establish fertility by any means following surgical sterilization have been unsatisfactory. However, surgery as a means of establishing fertility following tying and/or partial resection of the tubes has met with somewhat better results. This is true when the fimbriated ends of the tubes have been left intact, the tubes being tied and/or resected at the uterine end. This subject is separate and distinct from plastic operations on the tubes following pelvic disease.

Hayes⁶ reported a case of normal full term pregnancy following tubouterine implantation. She was a quartipara, 25 years old, who had been sterilized four years previously by section and ligature of both tubes at the uterine ends. However, following the plastic operation and before the successful pregnancy, there was one spontaneous abortion. His technique was as follows. Two pieces of silkworm gut were passed per vagina through the cervix and into the uterine

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Addendum

This patient has not menstruated since Feb. 11, 1947, and the diagnosis of pregnancy has been made and confirmed since completion of this paper. This is her second pregnancy since tubouterine implantation.

Report of Case

This is the case of a white woman, aged 23 years. On Sept. 9, 1938, at the age of 15 years, she was committed to a State Home, as an "incorrigible." Shortly after commitment, surgical sterilization, section of Fallopian tubes, was performed, by consent and request of her mother. On Oct. 10, 1940, she escaped from this institution. She was then 17 years old. She was not recommitted and the State officially discharged her. She was placed on parole.

During the summer of 1943, she consulted us and wished to be operated upon to re-establish fertility, since she wanted a baby. History was obtained from the institution, so the condition of the tubes was not investigated by insufflation nor by uterograms. She was operated upon at St. Mary's Hospital on Jan. 11, 1944. A tubouterine implantation was done, right tube only (technique to be described later). At that time, she was not with her husband due to war conditions. Her husband returned during December, 1945. She had not been with him since her operation. After his return, her next menstrual period began Jan. 12, 1946, and ended 4 days later. She was seen on Feb. 27, 1946, and pelvic examination showed a probable pregnancy. On Oct. 21, 1946, after a normal pregnancy, she gave birth to a normal 7 pound 11 ounce baby boy. It was a normal delivery.

Before operating upon her, we secured proper legal advice and a written release from the institution. The release was granted by the superintendent of the Home, on recommendation of the Social Service Department. The release stated that she was well adjusted.

Technique of Operation

Under general anesthesia, the abdomen was opened by a long right paramedian incision. Only a few adhesions were encountered and these were easily separated. The uterus was normal and in good position. Both tubes had been severed at the uterine juncture and a section of each tube had been removed. Both ovaries were present and normal. Both tubes were open at the fimbriated ends. The left tube was only about one-third its normal length and a probe inserted through the fimbriated end readily went to the closed proximal ligatured end where a section had been removed. It was at once apparent this tube was too short to be mobilized sufficiently to reach the corresponding cornu easily. It was therefore decided not to do a tubouterine implantation on this side. The right tube was one-half to two-thirds its normal length and a probe was easily inserted through the fimbriated end to the closed proximal end. This end was amputated and the probe then ran through the entire length of the tube. This end was then mobilized for a distance of three to four centimeters. A small wedge-shaped piece of the cornu was then removed, by transverse incisions, the incisions being carried down to and through the endometrium. The endometrium was now grasped by two Allis forceps and pulled partly through the uterine ostium just made. Two silk sutures were inserted through the open end of the tube, on opposite sides from the lumen to the outside. Each suture was then threaded on a large curved needle, both ends of the suture being put through the eye of the needle, and each needle was inserted through the uterine ostium and into the cavity of the uterus and then through the uterine wall. The sutures were brought out through the uterus on opposite sides of the ostium, to keep the end of the tube patent, and secured to the peritoneal covering of the uterus. The endometrium was then loosely sutured around the tube with No. 00 chromic atraumatic suture and the myometrium was next sutured loosely around the tube, the sutures catching the peritoneal covering of the tube. These sutures were not pulled tight so as not to constrict the tube. There was a normal convalescence, menstruation was normal, and pregnancy took place as above outlined.

Conclusion

A simple operative technique of tubouterine implantation is described with subsequent normal pregnancy. Although pregnancy is infrequent following plastic pelvic surgery to restore fertility, we believe it is justifiable and should be done in selected cases.

Material and Method of Study Used

The oxidized cellulose utilized in this clinical trial was supplied in sealed glass jars which contained 10 yards of $1\frac{1}{2}$ inch wide sterile gauze in 4 thicknesses. This material differs from ordinary gauze only in that it has a lemon yellow tint and carries a faintly acrid odor. When ready to be used, the seal was broken and the contents immediately packed into the uterine cavity. The processed gauze is comparable to the plain type in facility of handling. In contact with blood, the gauze quickly turns black, and, when used in quantity, forms a sticky, gelatinous mass.

That there is an appreciable decrease in volume in this process is illustrated by experiment in vitro. A 50 cm. cylinder was tightly packed with dry oxidized cellulose and enough whole blood was added to produce saturation. Twelve hours later, the mass occupied only four-fifths of the cylinder capacity.

The cases presented in this series were selected from admissions to the Obstetrical Department of the University of Nebraska Hospital. Patients were carefully screened to eliminate those exhibiting frank or potential infection. A total of 24 patients were packed, including 6 primiparas and 18 multiparas. Labors varied in length from one and one-half to twenty-eight hours, and all were uncomplicated in the first and second stages. Deliveries were normal and spontaneous in all but one case, in which low forceps were employed. The membranes ruptured a minimum of four minutes and maximum of seven hours prior to delivery.

In this small series, postpartum blood loss exceeded the normal in three patients, one of whom suffered an inversion of the uterus. The value of this study would have been considerably enhanced if postpartum hemorrhage had been a complicating feature of all cases reported, but we were particularly anxious to observe the local and general clinical reaction when oxidized cellulose was used as a postpartum tampon.

All packs were inserted by one of the authors, immediately following routine postdelivery inspection of the cervix. Amounts of gauze introduced varied from four to ten yards, and, in each instance, attempt was made to fill the uterine cavity tightly and completely. In the majority of cases, the Holmes uterine packer was used, but, in a few instances, the procedure was accomplished with uterine dressing forceps. Oxytocies were employed according to the departmental routine, which includes one c.c. of Pitocin administered intramuscularly at time of delivery of the anterior fetal shoulder, followed by giving $\frac{1}{320}$ Ergo-trate intravenously at termination of the third stage.

On the fifth postpartum day, all patients were prepared for and subjected to sterile vaginal examinations, noting presence or absence of pack residue. In addition, routine endocervical cultures were taken and residual urine measured. On the tenth postpartum day the examination was repeated and all vaginal remnants of the pack removed. Sedimentation rates, according to the Wintrobe method, were read on the day of delivery and again on the fourth and tenth postpartum days. The character and amount of lochia and the rate of uterine involution were observed and recorded daily. Postpartum nursing care was routine. Early ambulation is the rule on this obstetric service and no exception was made for patients in this study. Accordingly all cases were up in a chair on the second postpartum day. Those with uncomplicated course were discharged on the tenth day following delivery.

Results

Elimination of Pack.—Animal experiments had led the authors to believe that the cellulose packs might be retained until completely absorbed. It was soon

OXIDIZED CELLULOSE USED FOR INTRAUTERINE POSTPARTUM PACKING

Preliminary Clinical Report

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OXIDIZED cellulose,* the material used in this clinical study, is an absorbable, hemostatic, gauzelike material first prepared by Kenyon and associates.^{1, 2} They demonstrated that when ordinary surgical gauze or cotton is treated with nitrogen dioxide gas, the cellulose is converted into polyandroglycronic acid which is a soluble, hemostatic chemical compound, the end product retaining the physical form of the original gauze. This timely discovery led to extensive animal experimentation by Frantz³ in which oxidized cellulose was introduced into almost every cavity of the body. The absorbable and nonirritating properties of the material were clearly and conclusively demonstrated. When it was further discovered that oxidized cellulose was actively effective in controlling hemorrhage, unlimited usefulness was envisaged and clinical investigation was launched.⁴ The results were extremely gratifying, and demonstrated that it could be used safely and with impunity as a hemostatic pack in both open and closed cavities.

The success of its trial in the fields of general, urologic, gynecologic and neurosurgery⁵⁻⁹ suggested to the senior author that it might well be the answer for control of the ever troublesome and constantly dangerous condition of postpartum hemorrhage. Preliminary investigation in animals was begun in the Physiology Department of the University of Nebraska in collaboration with Dr. A. R. McIntyre.¹⁰

Female dogs, both pregnant and nonpregnant, were hysterotomized and a maximum of 5 yards of oxidized cellulose was packed into the endometrial cavity of one horn of the bicornute uterus. Ten days later the dogs were reoperated upon and the uterine cavities inspected, at which time portions of the endometrium were obtained for biopsy. The results of these experiments indicated no generalized toxic or pelvic inflammatory reaction. The absence of the original oxidized gauze at the time of reoperation further demonstrated that the gauze either had been completely absorbed or extruded through the birth passage. Biopsies obtained from the packed and opposite horns of the uterus revealed an identically normal postpartum histologic appearance. The conclusion, that oxidized cellulose may be used safely as an intrauterine surgical packing in animals, encouraged the authors to attempt its use in the human postpartum uterus.

*The oxidized cellulose (Hemopak) used in this study was generously and kindly supplied by Johnson & Johnson Company.

there appeared to be no excessive or diminished amount of discharge. The type of lochial discharge was difficult to ascertain because it was colored by contact with the packing residue. As indicated in Fig. 2, it was considered that the rubral discharge persisted beyond the accepted normal length of time in 14 cases; remained for the normal average in 9 cases; and disappeared sooner than normally expected in 1 case.

Rate of Uterine Involution.—Daily measurements of the height of the fundus were made on all patients. Measurement was in terms of number of fingerbreadths separating the fundus from the level of the umbilicus. In comparison with accepted standards,¹³ the results suggested that the rate of involution was slower than normal in 21 of the patients and within normal limits for the remainder. (See Fig. 3.) It appeared that intrauterine and intravaginal retention of the pack delayed the rate of involution by acting as a mechanical barrier to descent of the uterus into the pelvis.

Urinary Retention.—The patients experienced difficulty in voiding during the time that the pack remained in situ. However, in no case was absolute inability to void encountered. Catheterization for residual urine demonstrated that a total of 10 patients carried amounts of more than 50 c.c. on the fourth postpartum day. Of these, the residual persisted until the day of discharge in 5. No clinical or laboratory evidence of urinary infection was observed.

Bacteriologic and Histologic Study.—At the time of the routine examination of the fifth and tenth post-partum days, intercervical cultures were obtained. Bacteriologic study indicated the isolation of the following organisms in the frequency listed:

| | |
|---------------------------------|----------|
| Nonhemolytic streptococci | 15 cases |
| Escherichia coli | 14 cases |
| Staphylococci | 9 cases |
| Hemolytic streptococci | 6 cases |
| Monilia | 6 cases |
| Aerobic streptococci | 5 cases |
| Hemolytic staphylococci albi | 4 cases |
| Nonhemolytic staphylococci albi | 4 cases |
| Diphtheroids | 4 cases |
| Gram-negative rods | 4 cases |
| Staphylococcus citreus | 1 case |
| Streptococcus viridans | 1 case |
| Micrococcus tetragenus | 1 case |
| Bacillus subtilis | 1 case |
| Proteus vulgaris | 1 case |

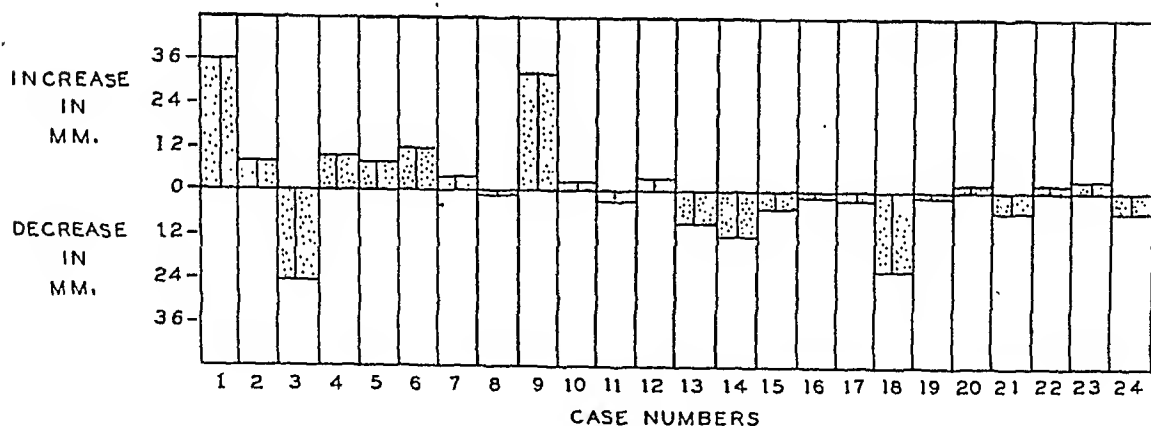
Inspection of the pack residue immediately upon expulsion gave evidence of a thin film of fragile, pink-colored, coagulum adherent to its surface. Representative sections were studied microscopically but in no instance was it possible to identify any decidual tissue.

Discussion

The merit of ordinary gauze as an intrauterine pack for the control of postpartum hemorrhage has long been established. The advantage of a similar material with the additional properties of absorbability and hemostasis is apparent. This clinical trial has served to gather clinical data concerning the intrauterine use of oxidized cellulose.

discovered, however, that the uterus treated the material as a foreign body and, by virtue of its contractile power, expelled the contents into the vagina within 72 hours following introduction. Expulsion from the vagina was complete in seven cases, among whom six were multiparous patients with marked perineal relaxation. Only one primipara expelled the pack completely and spontaneously. In each of these cases, the material extruded was in the form of a solid, tarry black, irregularly spherical bolus about 12 cm. in diameter. When teased apart, the central portion was found to retain the meshlike characteristic and color of the original cellulose gauze but without its tensile strength. In the remainder of the series, the pack was expelled into the vagina from which it was necessary to extract it digitally. The procedure was in no manner difficult and produced no unusual discomfort to the patient. Since oxidized cellulose is soluble in a 0.15 molar alkaline solution, it was considered likely that a sterile soda douche of such concentration might aid in expulsion. This was tried in one case with no appreciable effect. It was of interest to note that the surface of the expelled pack residue was smooth and indicated no evidence of attached endometrial tissue.

Morbidity.—All patients, who on two or more successive days, demonstrated a febrile reaction of 100.4° F. or higher were classified as morbid. Two such cases occurred within this series. One followed a complete inversion of the uterus with severe postpartum hemorrhage and shock, which was treated by immediate manual replacement of the uterus and introduction of an oxidized cellulose pack. The control of hemorrhage was not immediate, but the patient responded to substitution and replacement therapy and recovered completely. The cause of the morbidity encountered in the second case could not be explained. This represented a morbidity incidence of 8.3 per cent which compares favorably with the results of Anderson et al.¹¹ who reported an incidence of 38 per cent in a similar type of clinical study using gauze packs impregnated with sulfanilamide.



SEDIMENTATION RATE

Fig. 1.

Sedimentation Rate.—The value of this laboratory procedure was questioned, inasmuch as the rate is increased normally during pregnancy; however, a relative evaluation was attempted by obtaining a base level reading on the day of delivery and repeating on the fourth and tenth days post partum. As indicated in Fig. 1, there was an increased sedimentation rate of 5 mm. or more in 6 cases; no appreciable change in 14 cases; and a decrease in 4 cases.

Lochia.—The type and amount of lochia was observed carefully and classified according to standards described in current obstetrical texts.¹² In this study,

The results indicate that the material can be used without deleterious effect upon the patient. It produces no toxic or inflammatory reaction in the tissue with which it has contact, and on expulsion, does not carry with it any of the endometrium as does the regular type gauze pack, and so it may be considered atraumatic. There is always danger attendant to the invasion of the uterus and the same caution in sterile technique must be exercised in the introduction of this type of pack as in the use of any other.

The hemostatic property of oxidized cellulose has been adequately demonstrated in other experimental and clinical studies. In the three cases of postpartum hemorrhage encountered within this series, it proved effective in controlling blood loss. Its action is dependent upon direct apposition to the bleeding surface, and, for that reason, oxytocics were employed in an effort to maintain uterine tone and keep the uterus firmly contracted about the pack. For the same reason, it is important that the uterine cavity be tightly, firmly, and completely filled with the packing material, since the total volume of the residue is diminished following saturation with blood. This, of course, suggests that some of its effectiveness might be attributed to simple mechanical pressure.

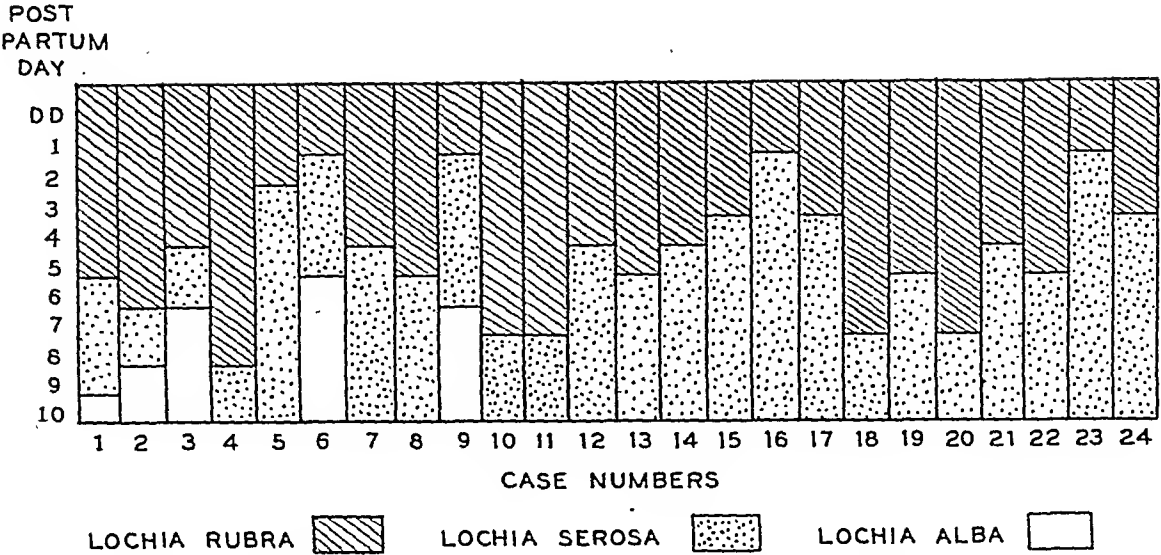
In anticipating complete absorption of the pack, sufficient consideration was not given to the fact that the quantity of material used required more time for dissolution than allowed by a contracting organ with a physiologic determination to rid itself of any foreign substance. The end result proved uterine elimination to be early and complete, but when retention within the vaginal canal did occur there was no difficulty in removing the residue with the sterile gloved index finger.

Subjectively, the patients complained frequently of discomfort due to pelvic pressure, especially during the time that the entire pack residue remained incarcerated within the vagina. As far as could be determined, the degree of pressure was no greater than that experienced by patients with regular gauze packs. Certainly, use of oxidized cellulose eliminated completely the distress that patients usually experienced with the removal of regular gauze packing material.

Time has not allowed for a complete follow-up on menstrual habits of the patients treated in this study, but, to date, there is no record of unusual disturbance in type, quantity, or regularity of catamenia when re-established.

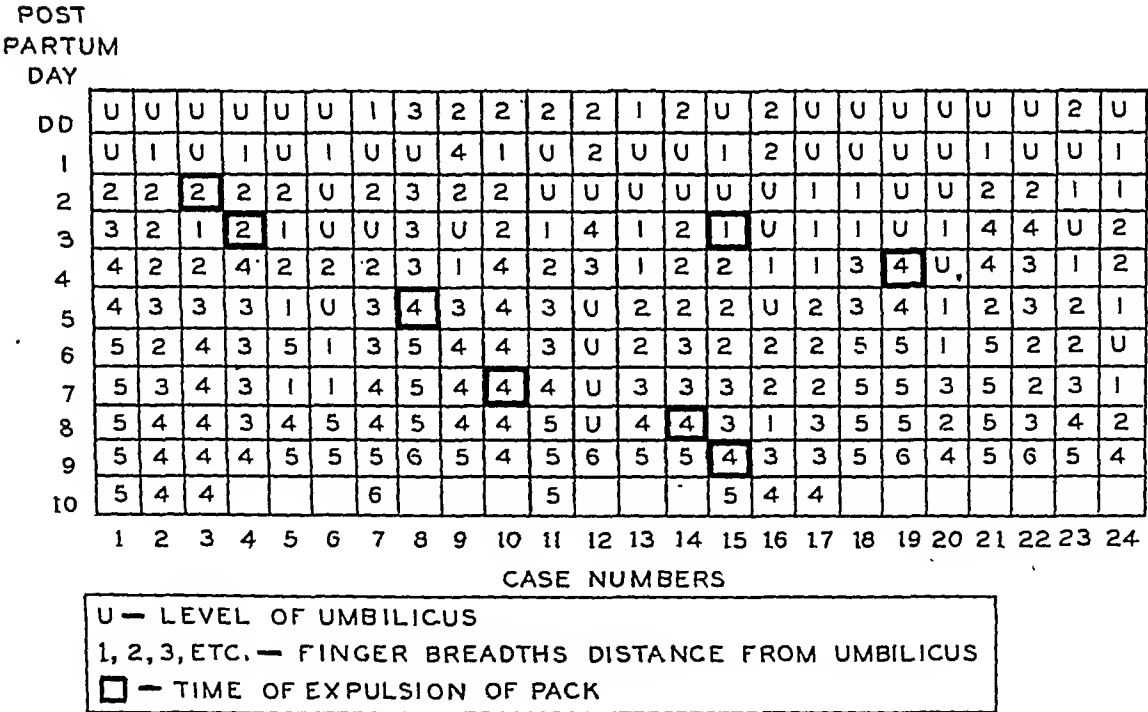
Summary

Oxidized cellulose in long strips was used as a postpartum intrauterine pack in twenty-four patients, of whom three demonstrated frank postpartum hemorrhage. Results obtained indicated that this type of packing is effective in the control of bleeding and has no harmful effects, either locally or generally. The gauze is spontaneously expelled by the uterus too soon to allow for complete absorption. This study serves to demonstrate that the gauze can be safely introduced into the postpartum uterine cavity to control postpartum bleeding. This represents a preliminary report and a larger number of cases are required for study before further conclusions can be drawn.



TYPE OF LOCHIA

Fig. 2.



RATE OF INVOLUTION

Fig. 3.

Department of Reviews and Abstracts

Selected Abstracts

Gynecologic Operations

Wharton, Lawrence R.: The Indications for Hysterectomy in Benign Conditions Near the Menopause, *South. M. J.*, p. 1013, December, 1947.

The decision for hysterectomy in many benign conditions of the uterus tests the diagnostic acumen and sound judgment of the gynecologist. Near the menopause, a variety of conditions may make accurate diagnosis of uterine pathology difficult. Obesity, apprehension with consequent rigidity of the abdominal wall are indications for careful pelvic examination under anesthesia.

The findings of Miller are quoted, to the effect that a review of hysterectomies done in 10 different hospitals during the first ten months of 1945 revealed that the clinical diagnosis was confirmed by the pathologist in 49.6 per cent of patients upon whom hysterectomy was performed. The clinical diagnosis was in error in 17.4 per cent but the operation was considered to be justified on the basis of pathology found. In 32.8 per cent there was either no pathologic lesion in the pelvic organ or the tissue diagnosis indicated that the operation had been contraindicated. Accuracy in diagnosis and soundness in judgment are under greater tests now than ever before because more women consult the gynecologist at the first appearance of symptoms or even when no symptoms are present. In such patients, error can often be avoided by a period of watchful waiting during which diagnostic signs will develop or laboratory tests will become positive. A plea is made for gynecologists to restrain the surgical hand where indications for operation are doubtful and thus increase the accuracy of diagnosis and avoid operation on those patients suffering from limiting functional disorders.

WILLIAM BICKERS.

de Senarclens, François: Coeloscopy and the Ovarian Cycle, *Gynaecologia* 123: 220-237, 1947.

The author, working in the Gynecological Laboratory and the Gynecology Clinic of the Paris Medical Faculty, used the Palmer technique for direct visualization of the ovaries. After a pneumoperitoneum of 4 to 5 L. of gas, 95 per cent oxygen and 5 per cent carbon dioxide, at the rate of 400 c.c. per minute, with the patient in Trendelenburg position, a small incision is made, with local anesthetic, centrally about 4 cm. below the umbilicus.

The authors discuss the contraindications of the procedure and the incidental and accidental complications arising from the use of the peritoneoscope. Ten cases are reported in the article. All cases were examined as near to period of ovulation as could be determined by history, nature of cervical mucus, and basal body temperature curve, and an endometrial biopsy was done the same day as the celioscopy.

In seven of the ten cases, de Senarclens found correction of the peritoneal findings with other data suggesting ovulation. He concludes that celioscopy is useful in sterility studies and treatment as well as being valuable in other menstrual abnormalities; e.g., endometriosis. The author does note, however, that Palmer, in the same laboratory, was able to visualize the whole ovaries in only 15 of 40 cases due to changes in the appendages.

C. E. FOLSONE.

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portion of the vagina is removed carcinoma cannot recur at that site. Surgery also removes the lymph nodes in the pelvis. Lymph node metastasis may be present even in early carcinoma of the cervix (stage I).

Dr. Harry H. Bowing discusses the use of intracavitary radiation therapy for carcinoma of the uterine cervix. The author uses a standard platinum tube containing 50 mg. of radium sulfate. The walls of the tube are 1 mm. thick. The applicator may contain one or more tubes. The following factors are approximate for the treatment of the average stage III lesion. The time of the application may vary from three to twenty-four hours. The dose ranges from 300 to 2400 mg. hr. The interval between applications is one to seven days. The total time consumed may be ten to twenty-one days. The treatment area is divided into zones and the dose applied to each zone in milligram hours is as follows: to the vaginal zone, 2100 mg. hr., to the proximal cervical zone, 1400 mg. hr., to the distal cervical zone, 1400 mg. hr., and to the intrauterine zone, 2000 to 2400 mg. hr. Roentgen therapy is started a few days before radium therapy is completed. A dose of 500 to 700 r is applied to each field. The author feels that the intracavitary intensive broken dose method of radium treatment, followed by supplemental roentgen therapy furnishes a wide range of individualization for the greatest number of patients who have carcinoma of the uterine cervix.

Interstitial radium therapy is presented by Dr. George W. Waterman. The author feels that the use of needles of low intensity radiation gives one the opportunity of using small doses over a long period of time. The method is also very flexible and can be adapted to all types and conditions of cancer of the cervix. No unusual conditions have been encountered with sepsis, fistula formation, or intestinal injury. The five-year survival rates compare favorably with figures presented for other forms of therapy for carcinoma of the cervix.

Dr. J. A. Del Regato discusses transvaginal therapy with x-ray. The author has treated over 200 cases of carcinoma of the cervix of all stages and none of these have received radium. This treatment has followed external radiation. The author has no five-year survival rates but he does have a 42 per cent three-year survival rate.

Dr. E. L. Jenkinson and associates give their five-year survival rates in treatment of carcinoma of the uterine cervix. Of 75 patients followed, 30.6 per cent were alive and free from disease after at least five years. In the breakdown by stages these figures are more enlightening.

Dr. E. L. Ernst discusses improvement in methods of intravaginal roentgen and radium therapy. He describes several types of expanding colpostats which give a more uniform type of radiation in the fornices. For transvaginal x-ray therapy the author prefers the use of a translucent plastic intravaginal cone.

WILLIAM BERMAN.

Michaels, John P.: Study of Ureteral Blood Supply and Its Bearing on Necrosis of the Ureter Following the Wertheim Operation, *Surg., Gynec. & Obst.* 86: 36, 1948.

This paper deals with the blood supply of fourteen ureters from seven premature infants which were dissected following the arterial injection with liquid latex. The blood supply in these ureters consists of one or more fairly large arteries which are derived from the abdominal aorta, the common iliac, or the internal iliac arteries. These ureteral vessels may be single, double, or triple. The long arteries, on reaching the ureter, divide into ascending and descending branches which anastomose freely with the short branches from the renal or occasional ovarian or spermatic arteries and with short branches from the vesicle and uterine arteries from below. A brief historical review of the Wertheim operation is given and the incidence of damaged ureter cited. In order to prevent ureteral injury, the author suggests a more proficient knowledge of the normal and abnormal blood supply of these structures, more careful dissection, and care in avoiding mass ligation.

L. M. HELLMAN.

Gurskis, Eugenia E., Beaver, Donald C., and Nelson, Harry M.: The Microscopic Criteria for the Diagnosis of Early Carcinoma of the Cervix Uteri, *Surg., Gynec. & Obst.* 85: 727, 1947.

This paper is a morphologic study of noninvasive and early invasive carcinoma in fifteen cervixes. Four thousand fifty-four biopsies were examined, taken from the microscopic slide

Levi, Alexander A.: Ovarian Conservation During Surgery With Reference to Bilateral Dermoids and Endometriosis, *New England J. Med.* 238: 83, 1948.

The author states that this paper was written to call attention again to the benefits to be derived from conservative operations upon the ovaries of young women who have bilateral dermoid cysts or endometriosis of both ovaries and even endometrial implants in the cul-de-sac, bladder, and Fallopian tubes. His experience in conservative ovarian surgery is based on seventeen years of gynecologic practice and he is convinced that conservative ovarian surgery is possible and ultimately pays large dividends to the patient.

The author presents in detail the operative findings, pathologic reports, and his particular method of conserving ovarian tissue when dealing with bilateral dermoid cysts of that organ in young women, in whom the childbearing function was not impaired by surgery.

He also gives in detail again his conservative surgical treatment of extensive endometriosis in young women in whom a pregnancy subsequently occurred. JAMES P. MARR.

Labor, Management, Complications

Barnes, Josephine: Pethidine in Labour: Results in 500 Cases, *Brit. M. J.* 1: 437, April 5, 1947.

The chemistry and pharmacology is reviewed. It is concluded that Pethidine (Demerol) has analgesic and antispasmodic properties. There are a fall in blood pressure and depression of respirations when large doses are employed. It was employed in 500 selected patients in labor, the great majority of whom were primiparas. It was considered a safe drug, as minimal toxic symptoms were noted in only eleven patients. The gross fetal mortality was 4.2 per cent. None of the fetal deaths were attributed to the use of Demerol. Although 55 infants showed some signs of asphyxia, all recovered. Some relief (analgesia, sleep, feeling of restfulness, and relaxation) was experienced in 87 per cent of patients and good analgesia was obtained in 55 per cent. Failure to obtain satisfactory analgesia was attributed to inadequate dosage or delay in administration. No significant effect on uterine contractions was observed but, in this selective group, labor was somewhat longer than in the controls. This observation does not support the contention that this agent shortens labor. The operative incidence was not increased. No significant amnesic effect was noted.

Pethidine is evaluated from the point of view of the ideal criteria laid down by Sturrock and, although it does not fulfill all his criteria, it is suggested that it approaches the ideal more nearly than any other obstetric analgesic drug in current use. R. G. DOUGLAS.

Malignancies

Ernst, Edwin C.: Diagnosis and Treatment of Carcinoma of the Uterine Cervix, A Panel Discussion. *Radiology* 49: 4, 1947.

Different phases of the subject are discussed by different men. Dr. A. N. Arnason discusses the clinical diagnosis of carcinoma of the cervix. He divides his cases into the infiltrating type, the evverting type and the cratered type of lesion. The evverting type of cancer presents a favorable prognosis. They are, as a rule, radiosensitive and are usually diagnosed in a favorable stage of clinical advance. The infiltrating type is less radiosensitive. It has a poorer prognosis and the disease has usually advanced to an unfavorable stage by the time the diagnosis is established. The cratered lesion may result from either of the previously mentioned types. Different types of x-ray therapy are mentioned for the different types of lesions. Reference is made to the value of radical hysterectomy.

The pathological aspects are discussed by Dr. Walter J. Seibert. The different forms of pathologic classification are reviewed.

The surgical aspects of the disease are discussed by Dr. John Brewer. Surgical treatment of cancer of the cervix is limited to stages I and II (League of Nations). Removal of the cervix by surgery eliminates the possibility of a recurrence there, and since the upper

(1) To show that there is an agent in the rectal and mouth washings of cases of epidemic diarrhea of the newborn which produces a corneal reaction in rabbits and that comparable material from healthy infants does not produce a similar reaction.

(2) To prove that it is a virus, first by demonstrating that it will pass a bacteria-retaining filter, and second by showing that it can be carried through serial passages.

(3) To prove, by serological means, preferably by a neutralization test, that the agent is the cause of the disease.

The investigation followed the method of Buddingh and Dodd, and, to a lesser extent, is directed to discovering other methods of isolating and propagating a virus or viruses and to proving that they cause the disease. The work is far from completion, but the results are sufficiently interesting and the problem sufficiently urgent to warrant a preliminary report at this time.

They have found an agent in the rectal washings which causes keratitis in rabbits in 82 per cent of 45 cases of epidemic diarrhea.

The agent passes bacteria-retaining filters, can be passed in the rabbit cornea or chick-embryo, and is presumably a virus. However, conclusive evidence that the virus is the cause of the disease has not yet been obtained.

JAMES P. MARR.

van Creveld, S.: Nutrition of the Pregnant Woman in Relation to Malformations of the New Born, *Gynaecologia* 124: 299, 1947.

The author, in reviewing the literature of congenital malformations in animals as the result of faulty diet, is of the opinion that abnormalities encountered in the human fetus may also be due in part to dietary indiscretions.

The interest in dietetics at least goes back to the Chou Dynasty in China, as early as 1155 B.C., since the rituals include advice on diet for the pregnant woman. It has been only recently that Western Europe was concerned with the possible effects of diet on the fetus as well as the mother.

That nongenetic factors may be responsible is suggested by two facts. (1) In the case of cleft lip and palate, the frequency of familial occurrence varies from 5.7 to 44.5 per cent. (2) There is a report of nine pairs of identical twins in whom only one member of each pair revealed a cleft palate. Malnutrition as an etiological factor of cleft palate has been suggested before. In animals, the classic example of the jaguar in the Berlin zoo that had thirty-two young with cleft palate is cited. When the diet of the jaguar included warm meat (instead of cold, bloodless meat) she promptly produced twenty-five successive offspring with normal palates.

A fair sampling of controlled human cases from the literature are cited. The author reports that statistics are now being reviewed concerning the increased frequency of congenital malformations in Holland during the recent occupation, when pregnancy diets were notoriously insufficient and definitely below the accepted optimal nutritional requirements, which are given as between 2,600 and 2,800 calories.

EUGENE N. SCADRON.

Cathie, I. A. B.: Breast-Feeding in Erythroblastosis Fetalis, *Brit. M. J.*, p. 650, Oct. 25, 1947.

This study was conducted to determine any possible deleterious effects on the erythroblastotic infant from nursing. It is known that milk of mothers who have borne such babies is high in Rh antibodies. Investigations were carried out which showed that antibody is not readily destroyed by the gastric juice of infants. In addition, the ingestion of large amounts of serum high in anti-Rh titer was possible without detectable absorption. It was accordingly concluded that the weaning of infants with hemolytic disease because of the antibody content of the mother's milk is not justified.

R. G. DOUGLAS.

Lawler, S. D., and van Loghem, J. J., Jr.: The Rhesus Antigen C^w Causing Hemolytic Disease of the Newborn, *Lancet*, p. 545, Oct. 11, 1947.

The authors report the second case of isoimmunization due to the rare Rh antigen C^w, which is found in 2.5 per cent of English people and 4.9 per cent of the Dutch. Since the

files of the Women's Hospital in Detroit. Seven cases were selected as demonstrating early noninvasive carcinoma. In addition, eight other cases were obtained from other institutions. Six of the early noninvasive tumors demonstrated invasive carcinoma in other areas of the cervix. This paper contains no clinical follow-up and only microscopic comparison of the noninvasive tumors with early invasive carcinoma is used as a basis of diagnosis. The following were taken as the criteria for the diagnosis of noninvasive carcinoma: 1. The squamous epithelial cells had a decreased amount of cytoplasm with deeply stained oval nuclei. All fifteen cases showed this change. 2. All the cells of the epithelium resembled each other, from the basal to the uppermost layer, so that the basal was not distinguishable. This change was observed in twelve cases. 3. In all cases, there was an increase in the number of cells in the stratum germinativum. 4. Fourteen showed mitotic figures. 5. Basement membrane was not penetrated in any noninvasive case. 6. There was subepithelial lymphocytosis in all cases. 7. Seven cases showed Schiller's line of demarcation between the normal and malignant tissue. 8. All fifteen cases showed loss of polarity of the cells.

These fifteen cases seem to bear out the earlier work of Rubin, Meyer, Schiller, and Broders. The great lack in many papers on early noninvasive carcinoma has been the poor clinical correlation.

L. M. HELLMAN.

The Newborn

Caffey, John: Prenatal Bowing and Thickening of Tubular Bones, With Multiple Cutaneous Dimples in Arms and Legs. (A Congenital Syndrome of Mechanical Origin), *Am. J. Dis. Child.* 74: 543, 1947.

Prenatal bowing and angulation of a single tubular bone or of a pair of tubular bones have been reported in a small number of cases.

The author presents the case histories of three infants born of healthy mothers, each of whom had congenital symmetric bowings of the femoral and humeral shafts and similar, but sometimes unpaired, deformities of the shafts of the tibiae, radii, and ulnae. In each case, the bowed diaphyseal segments were thickened, as well as bent. All curvatures extended through substantial longitudinal segments of the shafts in or near their middle thirds. Large, symmetric cutaneous dimples overlay the salient angles of the curves in two of the three cases. In the third case, dimpling was not particularly looked for.

The infants were born of healthy mothers, and there was no evidence of inherited or familial skeletal or cutaneous disease. The infants were healthy. Complete x-ray studies are presented and described, also complete laboratory findings.

The cause and pathogenesis of these prenatal deformities cannot be established unless new methods of examination are introduced for their study. However, the author believes that the skeletal deformities can be explained satisfactorily in large part by prenatal mechanical disturbances in utero. In like fashion, pressure from the uterine wall on the fetal skin compressed on ectopic, exposed bony points of the fetus produced the cutaneous dimplings.

Many of the bony deformities disappeared with advancing age, especially in the upper extremities, but many others were still present during the third year of life. All neonatal dimples persisted during infancy without significant change with advancing age.

JAMES P. MARR.

Meiklejohn, Gordon: Viral Studies on the Etiology of Epidemic Diarrhea of the Newborn, *California Med.* 67: 238, 1947.

The investigation on the etiology of epidemic diarrhea of the newborn was carried on as a joint enterprise of the Virus Laboratory of the California State Department of Public Health and the Infectious Disease Laboratory at San Francisco Hospital.

Material was received from all parts of the state; however, material from five hospital outbreaks represented some 256 cases. Forty-nine proved fatal.

The general plan of investigation has been as follows:

Items

American Board of Obstetrics and Gynecology

The American Board of Obstetrics and Gynecology in annual session in Washington, D. C., May 16-22, 1948, announced the election of the following officers:

Walter T. Dannreuther, M.D., President, 580 Park Avenue, New York, New York.
Joseph L. Baer, M.D., Vice-President, 104 S. Michigan Avenue, Chicago, Illinois.
Norman F. Miller, M.D., Vice-President, University Hospital, Ann Arbor, Michigan.
Paul Titus, M.D., Secretary-Treasurer, 1015 Highland Building, Pittsburgh, Pennsylvania.

The other Directors of the Board are:

Willard R. Cooke, M.D., Department of Obstetrics and Gynecology, Medical Branch, University of Texas, Galveston, Texas.

F. Bayard Carter, M.D., Duke University, Durham, N. C.

Robert L. Faulkner, M.D., 2105 Adelbert Road, Cleveland, Ohio.

Daniel G. Morton, M.D., University of California Medical Center, San Francisco, California.

Robert A. Kimbrough, Jr., M.D., 807 Spruce Street, Philadelphia, Pennsylvania.

Dr. Morton was appointed to fill the unexpired term of Dr. Edward A. Schumann of Philadelphia, Pa., representing the American Gynecological Society, and Dr. Kimbrough the unexpired term of Dr. Ludwig A. Emge of San Francisco, California, representing the Section on Obstetrics and Gynecology of the American Medical Association. Both of these former Directors had found it necessary to resign.

At this examination meeting 231 candidates were certified.

A number of changes in Board requirements and regulations were made. New Bulletins are now available for distribution upon application, and give details of all new regulations. These relate both to candidates and to hospitals conducting residency services for training.

Foremost are the following:

- (1) The ruling that applicants must receive adequate training in both obstetrics and gynecology has been defined as meaning a minimum of six months, full-time, in the branch of either obstetrics or gynecology relegated to a minor role in a candidate's training and preference for practice.
- (2) Acceptable preceptorship training is defined.
- (3) The present regulation requiring at least six months of practice in the specialty following the completion of an acceptable training period, has now been extended, effective December 31, 1949, to a requirement of two years post-training practice limited to the specialty.
- (4) Specific requirements for approval of hospital services for residency training are outlined.
- (5) Effective immediately, there will be no further temporary approvals of hospital services for residency training. It is planned that all hospitals holding any type of residency training approval will soon either be resurveyed or initially surveyed by the Council on Medical Education and Hospitals of the A. M. A. so that all future approvals, new or old, will be based entirely upon inspection following application. It is expected also that certain resurveys will result in withdrawal of present residency approval from institutions where the educational and training standards are not being maintained.

parents and the erythroblastotic infant were alike in blood groups and in the common types of Rh antigen, the cause for erythroblastosis in this case was obscure at first.

IRVING L. FRANK.

Witebsky, E., Rubin, M. I., and Blum, L.: Studies in Erythroblastosis Fetalis: I. Activation of the Incomplete Rh Antibody by the Blood Serum of Full Term and Premature Newborn Infants, *J. Lab. & Clin. Med.* 32: 1330, 1947.

The authors discuss the properties of the "blocking" or "incomplete antibody" which requires albumin solution or undiluted serum as a diluent, rather than saline solution to activate its agglutination properties. By the use of sera from premature infants, full-term infants, and infants during the neonatal period, they have demonstrated a maturation of the capacity to activate this antibody. This property varies considerably, but in general is weak in serum of any infant in comparison to adult serum, and apparently is absent in the fetus until full term approaches. They discuss the clinical implications of this phenomenon and emphasize the danger of exposing the cells of an erythroblastic infant to adult serum and the advantage of replacing the infant's cells with exchange transfusion. They also suggest that this phenomenon of gradual maturation of the activating principle may lend some support to the proponents of premature delivery in erythroblastosis fetalis. S. B. GUSBERG.

Witebsky, E., Rubin, M. I., Engasser, L. M., and Blum, L.: Studies in Erythroblastosis Fetalis: II. Investigations on the Detection of Sensitization of the Red Blood Cells of Newborn Infants With Erythroblastosis Fetalis, *J. Lab. & Clin. Med.* 32: 1339, 1947.

This group of investigators discuss the importance of early laboratory support for the clinical diagnosis of erythroblastosis. In view of the fact that many clinically erythroblastotic infants show few or no free antibodies in their cord serum, the need for a test to determine sensitization of the child's red cells is evident. The authors propose a slide test for detection of such sensitization, which simply requires the addition of a drop of normal adult serum to several drops of the infant's packed washed red cells; adult serum has the capacity to activate agglutination in these sensitized cells. Experimental work demonstrating these phenomena is presented, and their clinical significance discussed. The authors re-emphasize the theoretical danger of adult serum when transfused into an erythroblastotic child. S. B. GUSBERG.

McBurney, Raymond: Full-Term Infant, *West. J. Surg.* 55: 363, 1947.

The California State Board of Health requires that all babies weighing 5 lb. 8 oz. or less be reported as premature. Evidence is presented to show that the birth weight is not necessarily indicative of the state of prematurity of the newborn; approximately 1 per cent of 6,641 babies born at term weighed 5 lb. 8 oz. or less. These babies are not premature but undernourished. The undernourishment may be the result of insufficient food supply to the fetus because of the small placenta, infarcts of the placenta, toxemias of pregnancy, or partial separation of the placenta. The mortality rate in this series of babies, designated as premature according to the law, was no higher than in any series of normal newborn babies. It is concluded by the author that birth weight alone is not sufficient indication of prematurity. S. B. GUSBERG.

Eller, William C.
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described more or less independent muscles, attributing their names to different fibers, which was the practice in their times, e.g., Wilson, Guthrie, and Muller who described special periurethral fibers.

No less an authority than Luschka described the transverse perinei as a part of the levator ani muscle while others considered it a completely independent muscle. However, Gegenbaur, in his textbook, laid it down "that a morphological unity of all the muscles of the perineum exists, inasmuch as they develop from the primitive sphincter cloacae muscle." This was the guiding principle which stimulated Popowsky in his research.

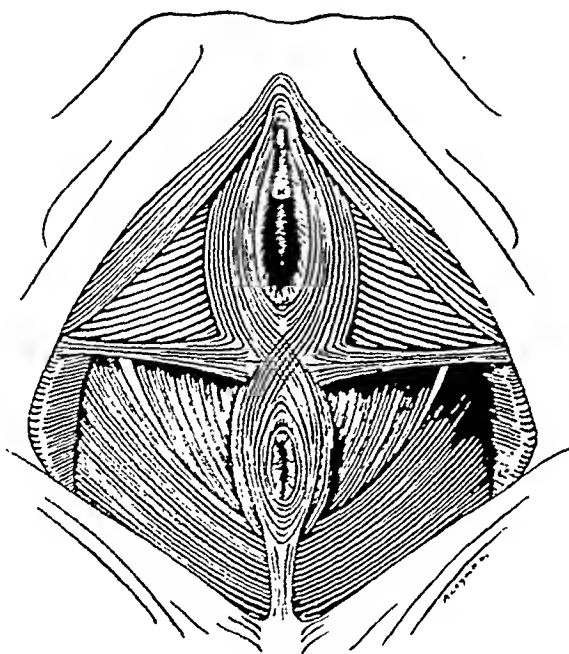


Fig. 1.—Schematic representation of the sphincteric muscular group of the pelvic floor. (Power, *Surg., Gynec. & Obst.*, Sept., 1946.)

Popowsky, working with a series of young embryos, term babies, and adults, was able to demonstrate the origin of the sphincteric vulval group as arising from a single subcutaneous muscle, the sphincter cloacae (Fig. 2). I have repeated a large part of this work in the anatomic laboratory of McGill University, and my results, as far as they go, confirm Popowsky's conclusions.

In the early embryo the allantois and the hindgut terminate caudally in a common cavity, the cloaca. This structure, of course, corresponds to that found in the adult reptiles and birds, in which the orifice is surrounded by a sphincteric muscle. In the human embryo the allantois becomes separated from the cloaca by the ingrowth of a transverse mesodermal bar, thus forming the rectum behind and the urogenital sinus in front. The sphincteric muscle as a distinct entity can first be seen in a two-month human embryo. For the most part, this primitive muscle completely surrounds the orifices of the urogenital sinus and anus, but already a few fibers can be seen to decussate between these

American Journal of Obstetrics and Gynecology

VOL. 55

MARCH, 1948

No. 3

*Transactions of the Second Annual Meeting
of the Society of Obstetricians and Gynecologists of Canada, Ste.
Marquerite, Quebec, October 27-29, 1946*

EMBRYOLOGICAL DEVELOPMENT OF THE LEVATOR ANI MUSCLE*

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BY WAY of preamble, it is relevant to dwell briefly on the anatomic arrangement and functional development of the vulval sphincteric musculature (Fig. 1). This muscular group derives its origin from the common cloacal sphincter to which the levator ani muscle is inextricably related. Both the cloacal sphincter and the levator ani are ultimately derived from the third and fourth sacral myotomes.

The morphological work of Eggeling (1896) and the embryological investigations of Popowsky (1899) have elucidated the relationships of the vulval sphincteric group. From the "primordial sphincter cloacae" there arises, both in the course of phylogeny and of embryology, a division into a sphincter ani externus and a urogenital sphincter. The sphincter ani may differentiate into several layers and become a trilaminar muscle. The urogenital sphincter also differentiates further, but in a more decisive manner. From it are developed the sphincter urethrae, the ischiocavernosus of either side, and a median bulbo-cavernosus retaining a tendineus raphe in the midline, and probably the transverse perinei, superficial and deep.

Difference of opinion exists regarding not only these latter muscles themselves but also the question as to where they belong, their isolation, and non-isolation. Among others, Henle and Gegenbaur recognized the existence of a single muscle placed around the membranous part of the urethra, while others

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

transverse perinei muscle is formed. The deep transverse perinei is the last of the perineal muscles to appear in the human embryo and most of its development occurs postnatally. These two muscles apparently represent a development from the sphincter vaginae.

Practically nothing is known of the origin of the urogenital diaphragm. In some of the lower apes the fascia on the caudal aspect of the pubo-caudalis muscle forms a diaphragm in this region, but it is very doubtful if this is homologous with the human urogenital diaphragm. Wesson showed that in early life the human urogenital diaphragm is poorly developed and later acquires its characteristic density and strength. He regards it as a functional development, arising in man consequent to the upright posture and formed by a condensation of the fascia surrounding the muscles. The muscle mass in the embryo is covered on both aspects by a primitive connective tissue and in response to the functional requirements of the area, these sheets of connective tissue probably differentiate into the strong fascial lines of the urogenital diaphragm.

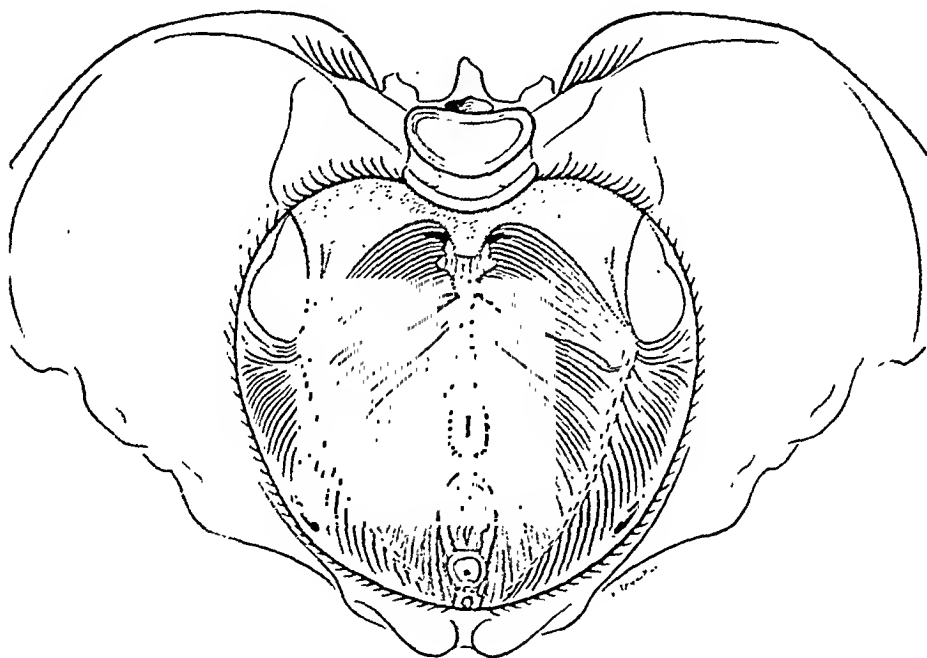


Fig. 3.—Levator ani muscle seen from above. Note anteriorly how pubococcygeal fibers are attached directly to the os pubis. Pubovaginalis and puborectalis fibers are clearly defined.

Davies describes the urogenital diaphragm as a continuity of the endopelvic fascia. This throws no light on its origin and is merely a statement that the various fascial layers in the pelvis are continuous with each other. This is a very usual phenomenon throughout the whole body.

In the lower monkeys the tail musculature is well developed and helps to support the viscera. It is composed of a strong pubocaudalis extending from the pubis to the tail and more laterally placed abductor caudalis muscles. The pubocaudalis passes beside the rectum but has no or only very slight attachments to it. In the anthropoids an anococcygeal raphe is present. The well-defined pubocaudalis finds some attachment to the rectum. The iliococcygeus and

two openings. The primitive cloacal sphincter is thus beginning to divide into a sphincter ani externus behind and a sphincter of the urogenital sinus in front.

With the sphincter ani externus we have no further concern. As already stated, it differentiates into a trilaminar muscle. Coming to the sphincter of the urogenital sinus, we may note that shortly after the sinus opens on the surface of the embryo, the ventral end of this muscle gains a slight attachment to the precartilaginous anlage of the os pubis. The ventral-caudal end of the urogenital sinus becomes differentiated into the urethra. Consequently, the ventral part of the urogenital sphincter develops into the sphincter of the urethra and migrates to a deeper plane. At a somewhat later date the conjoint caudal end of the Müllerian ducts which have made contact with the dorsal surface of the urogenital sinus push their way down along the posterior wall of the sinus to form the vagina; the dorsal end of the sphincter of the urogenital sinus surrounds the opening of the primitive vagina and differentiates into the sphincter vaginae or bulbocavernosus muscle. The sphincter of the urethra and the sphincter vaginae are still structurally continuous and are attached ventrally to the primitive pubis and from these the ischioecavernosus muscle develops.

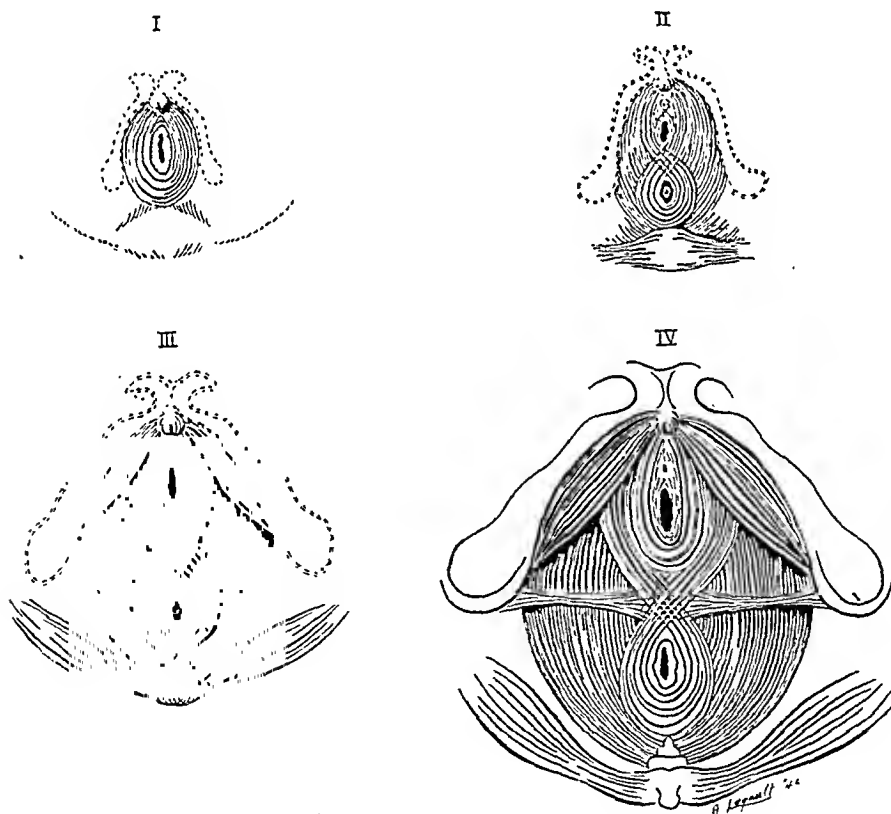


Fig. 2.—Successive differentiation of the cloacal sphincter in embryos of two, three, five, and seven months.

In the anthropoid apes the sphincter ani extends forward and forms a muscular diaphragm closing in the subpubic angle, and no true transverse perinei muscles are formed. In man this forward extension of the sphincter ani is not found, and instead we find that first a superficial and then a deep

segments is both phylogenetically and ontogenetically the oldest in the body. The development of many of the muscles in man and animals has never been traced and of the remainder our knowledge is fragmentary and incomplete.

The levator ani muscle is an evolutionary product representing the caudal flexor, abductor musculature of tailed mammals, which in man, as in anthropoid apes, with the reduction of the tail, has gained new relationships with the pelvic viscera. The coccygeus represents the proximal ventral caudal abductor of tailed mammals. No effort to verify the former statement in the human fetus is recorded in the literature to my knowledge.

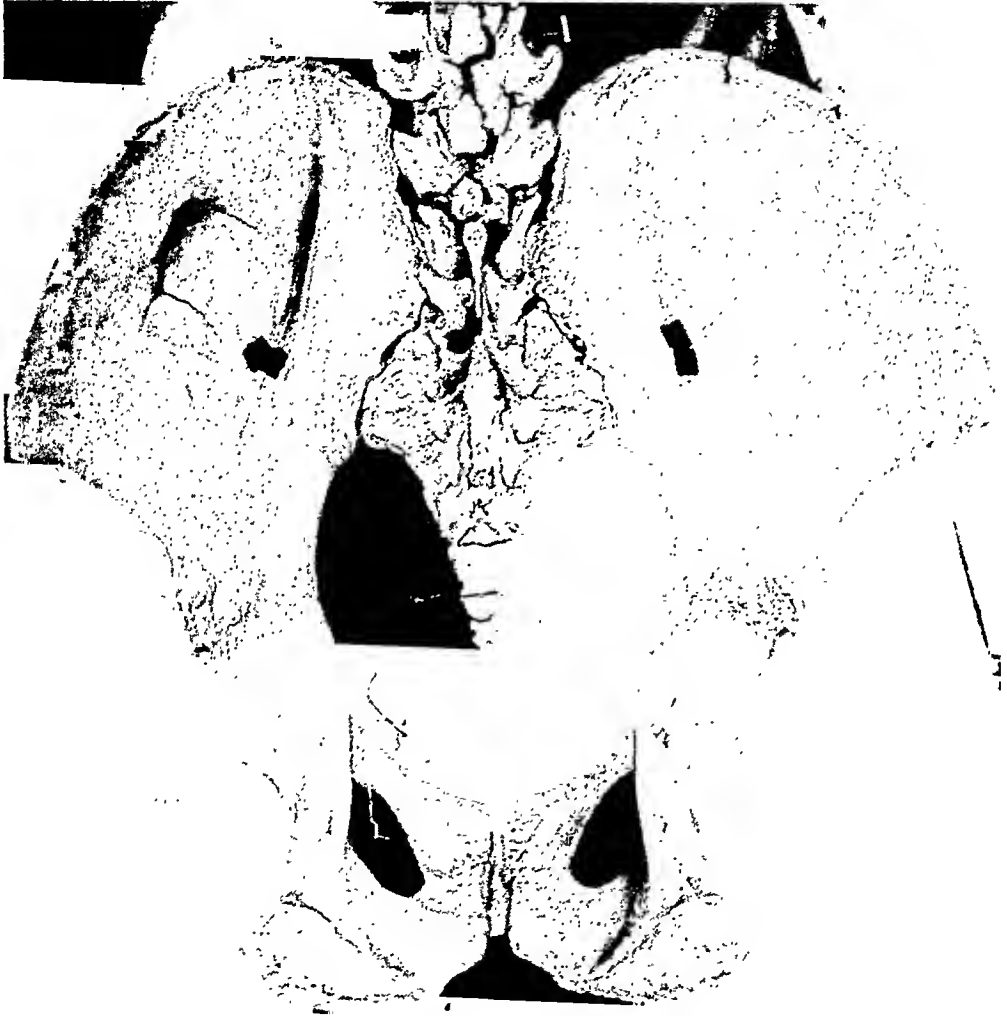


Fig. 5.—Gorilla's pelvis seen from behind.

Let us for a moment consider the recti group of the thoracoabdominal muscles which arise through the ventral extension of the thoracic myotomes into the body wall.

Certain fundamental processes are operative in the changes of the myotomes during the formation of adult muscles. Such processes may consist of a change in the direction or a migration of myotomes, fusion of portions of successive myotomes as in the formation of the rectus abdominis muscles, or a longitudinal or tangential splitting, or a degeneration of myotomes.

coccygeus show tendinous changes. In man the pubocaudalis attains its maximum attachment to the rectum and forms a true puborectalis, while the ilio-coccygeus and coccygeus show further muscular and fascial regression. In its morphologic development the pubocaudalis experiences a regression in muscular elements with a compensatory development of tendon and fascia (Fig. 3).

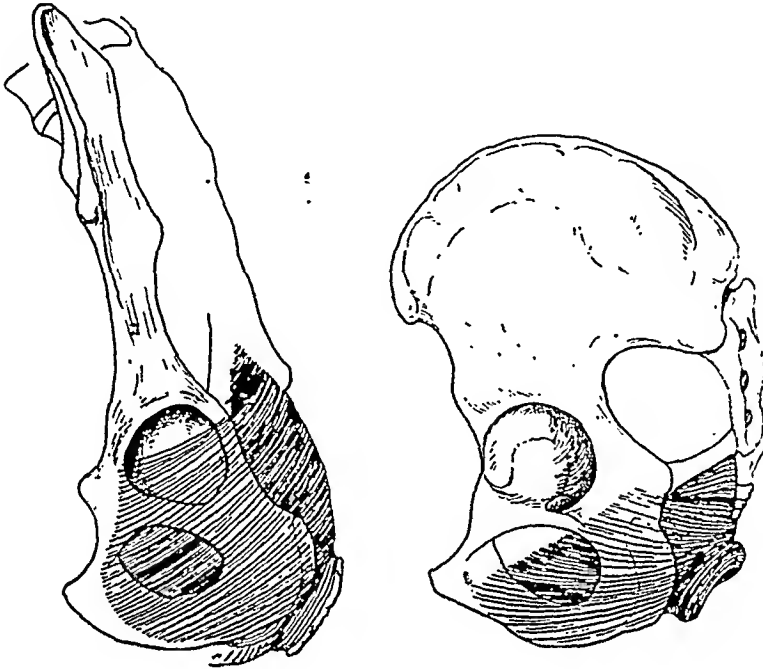


Fig. 4.—Lateral view of (A) great anthropoid, and (B) human pelvis. Note high cup-shaped arrangement of levator ani muscle in anthropoids with large external sphincter and cephalad termination of sacrum. In the human being the external sphincter is smaller and the triangular ligament is present, the sacrum is wider and terminates more caudally. Notice rotation of ilium in the human being.

To summarize, in the anthropoids the sacrum is situated very cephalad to the ischium; the pelvic outlet accordingly is a very elongated lozenge, the dorsal end being much cephalad to the ventral, and is weak, especially posteriorly. This is compensated for by an exceptional development of the sphincter ani externus which extends forwards as a muscular diaphragm into the urogenital area (Fig. 4). In man the bony pelvis is greatly shortened in a cephalic caudal direction and the wider sacrum terminates at a relatively lower level. The outlet, therefore, is very much shortened dorsoventrally, but is relatively broadened from side to side, especially in the anterior part. The pubocaudalis now is mainly attached to the rectum and anocecygeal body; the iliocecygeus has also moved its insertion on to the side wall of the anal canal and anocecygeal body, and the coccygeus muscle itself is more tendinous and forms the lesser sacrosacral ligament. Compare, for example, a gorilla with a human pelvis (Fig. 5). Notice in the gorilla how cephalad the sacrum terminates; the complete absence of an ischial spine; the absence of a true sacral notch, and the elongation of the whole pelvis as compared to the human being. In man the sphincter ani externus is much reduced and does not form a diaphragm, and in its place we find the deep and superficial transverse perineal muscles, and the urogenital diaphragm.

The skeletal musculature is derived almost entirely from the primitive segments. These may be said to begin with the segmentation of the dorsal divisions of the trunk mesoderm. The musculature arising from the primitive

The myotomes begin to grow into the body wall with the development and extension of the ribs. Even in a 7-mm. embryo, before the myotomes are fused into a continuous column, this process has already begun. In a 9-mm. embryo the myotome process extends further ventrally than do the ribs and ends ventrally in a continuous column on each side—the “rectus element” formed by the fusion of the entire myotome thickness.

This ventral longitudinal muscle column of each side ultimately forms the rectus abdominis and pyramidalis in the abdomen; the depressor muscles of the hyoid bone in the neck, while in thorax, owing to the development of the sternum, is not represented or is represented very occasionally by a vestigial sternalis muscle. At this early stage of the embryo we may note that the cloacal membrane is still on the caudal edge of the umbilical cord (Fig. 7). The primitive longitudinal ventral muscle column, therefore, extends between the two openings of the primitive alimentary canal; from the mouth to the primitive cloacal membrane. At a later stage the cloacal membrane migrates caudally into the perineum, and as it does it carries with it the original ventral cleft between the muscle column of either side. Thus are formed the lower part of the linea alba with the rectus abdominis muscles on either side.



Fig. 8.—X-ray photograph. Note absence of pubic element on right side.

The levator ani muscle, as shown by its nerve supply, is undoubtedly derived from the fourth sacral myotome, and it is tempting to suggest that as this myotome migrates ventrally it becomes divided like the myotomes of the abdominal wall, into two portions; a lateral part, the iliococcygeus, forming a continuous sheath and corresponding roughly to the oblique muscles of the abdominal wall; and a ventral longitudinal column, the pubococcygeus, or pubocaudalis of lower forms, corresponding approximately to the rectus abdominis. If this view is substantially correct, the anovaginal cleft between the pubococcygeus of either side really corresponds to an extension of the linea alba, which was later cut off from the abdominal linea alba by the development of the

As the body wall develops, extensions of the myotomes migrate ventrally into these walls and the ventral ends of these extensions fuse together to form a ventral longitudinal muscle column from which the rectus abdominis and other elements are ultimately developed (Fig. 6).

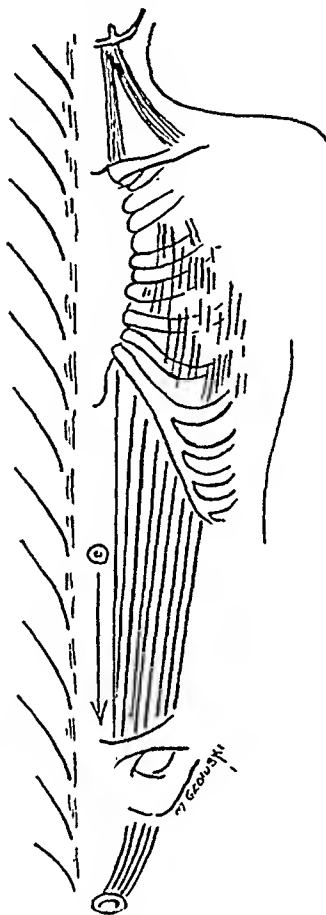


Fig. 6.—Right side undifferentiated ventral longitudinal muscle column.
Left side differentiated ventral longitudinal muscle column.

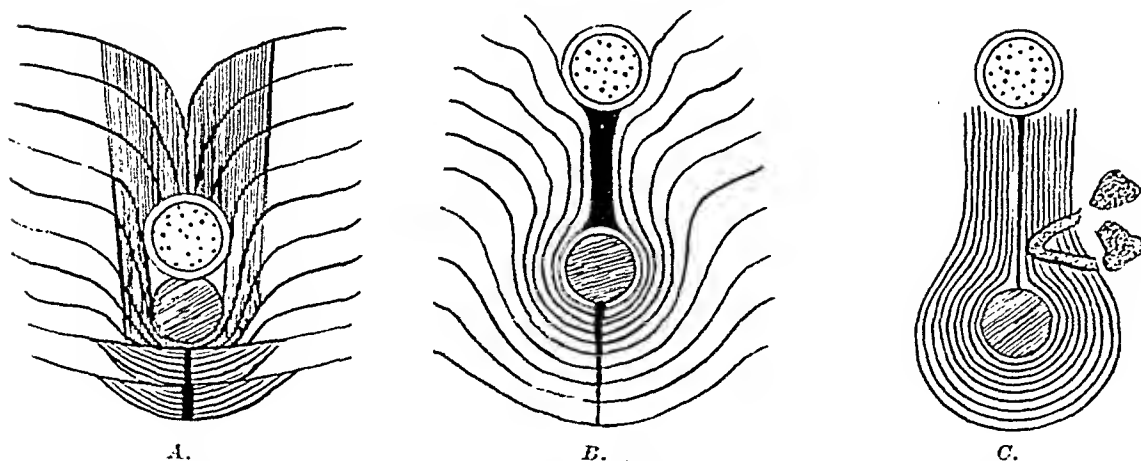


Fig. 7.—Diagrammatic representation of the formation of the lower end of the linea alba and the anovaginal cleft. A. The cloacal membrane extends onto the caudal surface of the umbilical cord. B. The cloacal membrane has migrated ventrally forming the upper end of the linea alba below the umbilicus. C. The cloacal membrane has reached the perineum. The pubic element growing in from the side cuts off the lower end of the linea alba to form the anovaginal cleft. (Dotted center represents the umbilical cord. Cross-hatched circle represents the cloacal membrane.)

to form a longitudinal muscle column on each side of the linea. This view of the structure of the levator ani muscle, which I owe to Professor C. P. Martin, means that the structure of this muscle presents many analogies with that of the anterior abdominal wall muscles.

Again, if this view is substantially correct we might expect that, in cases where the os pubis is absent, or imperfectly developed, the lower end of the rectus abdominis and the ventral end of the puborectalis ought to be structurally continuous. Through the kindness of the Pathological Department of McGill University, I was permitted to dissect a case of ectopiae vesicae in which the pubis was totally absent on the right side and was only represented by a small element on the left (Fig. 8). Figure 9 is a dissection of the right side of the abdominal wall and perineum. It shows the rectus abdominis passing without a break into the puborectalis. This terminates to the left of the coccyx. On the left side rectus abdominis fibers passed directly to the pubic element, while about halfway between the umbilicus and this element other



FIG. 10.—Transverse section, seven-week fetus, just beneath the pubic element. Some cartilaginous cells are present. On the left side note differentiation of pubococcygeal (*a*) and illococcygeal (*b*) fibers to the anterior face of the pubis. These fibers run obliquely caudalward in an anteroposterior direction.

fibers split and passed caudally in juxtaposition to and behind the large bowel, disappearing in the perineum posterolaterally to the displaced anus. The perineum was very short on the left and it was not possible to dissect the left puborectalis.

os pubis. The longitudinal muscle column of either side, therefore, still extends morphologically between the two openings of the alimentary tract, but is interrupted at two places—one, by the formation of the sternum, and two, by the formation of the os pubis. In other words, as the cloacal membrane migrates from the umbilical cord to the perineum it carries with it, so to speak, an extension of the linea alba, and also an extension of the tendency of the myotomes



Fig. 9.—Dissection of eviscerated fetus. Diagrams A, B, and C with fetus tilted at varying degrees show continuity of rectus abdominis fibers terminating in right puborectalis muscle. *a*, Rectus abdominis fibers. *b*, Puborectalis fibers.

In support of this view we may note that in the selacians, the pelvic floor is formed by a backward continuation of the rectus abdominis. (Kieth and Paramore, *Lancet*, May, 1910.) The pelvic part of the rectus is attached behind to the tail; anteriorly it is attached to the movable pelvic girdle. The cloaca of the dogfish passes out between the right and the left primitive representatives of the levator ani, which can compress the cloaca, not by depressing the tail, as in mammals, but by pulling the pelvis backwards. This would make the pubocaudalis simply a caudal continuation of the rectus abdominis element.

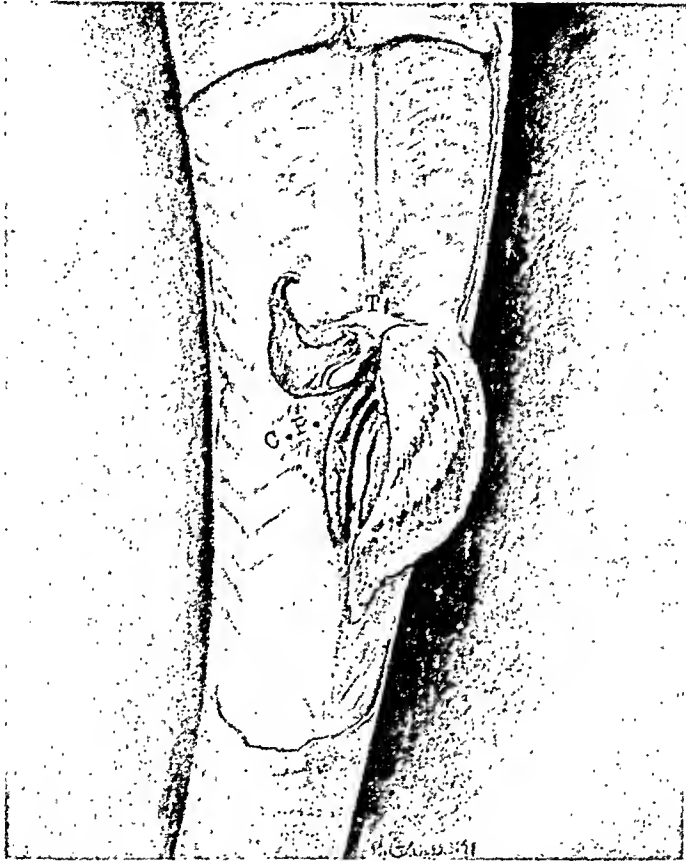


Fig. 13.—Drawing of adult dogfish, ventral surface. M = Myotomes. T = Transverse pelvic bar. C.P. = Caudopelvic strand.

A pelvic floor can scarcely be said to exist in the fish, for the pelvis is rudimentary. In the dogfish (Fig. 13) the pelvic girdle is represented merely by a transverse bar of cartilage placed in front of the cloaca. It is unconnected with the vertebral column except by means of that part of the lateral trunk musculature which extends forwards from the tail into the body and which, as it passes over the pelvic bar, sends a good strand of its lowermost fibers to be inserted into its upper and lateral part. This strand of fibers, which forms part of the central tail musculature, from which it cannot be differentiated, is directed from behind forwards to the pelvic bar and may be called the caudopelvic strand.

Efforts have been made to follow the development of these muscles in detail in the human embryo and are still under way. We are not yet in a position to make a positive statement as regards the human embryo, but we have many indications that lend support to our view (Figs. 10, 11, and 12).

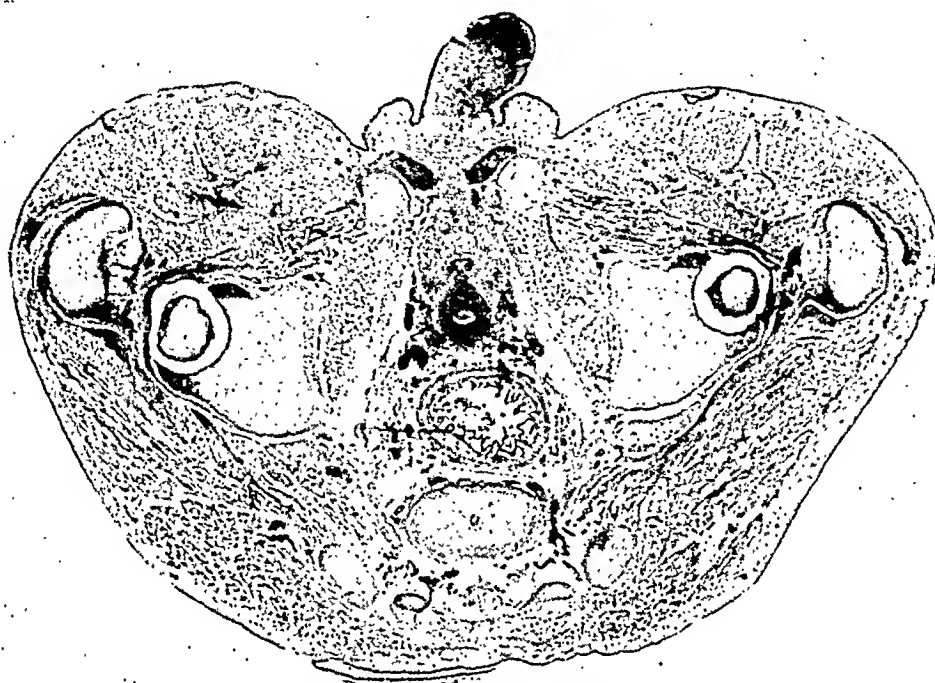


Fig. 11.—Two-and-one-half month fetus. Transverse section through acetabular region. Notice obturator internus muscle medial to which are the pubococcygeal fibers, extending antero-posteriorly.



Fig. 12.—Actual dissection of four-month fetus showing pubococcygeal and puborectalis fibers. In a younger fetus the caudal end of the vertebral column is almost vertically beneath the pubic element. Thus the puborectalis and rectus abdominis fibers are almost in a straight line.

Lastly, this way of looking at things may possibly help to explain such abnormalities as ectopiae vesicae and epispadias, for, if the cloacal membrane, in its caudal migration, developed abdominal adhesions in the region of the umbilicus it could well happen that a stretched and attenuated ventral wall to the allantois would be left in the linea alba and would subsequently rupture, forming an ectopiae vesicae. Moreover, when the genital tubercle began to form near the caudal end of the cleft, we can easily see that its ventral and cephalic surface might include the caudal end of this attenuated membrane. In the perineum, however, the deficiency in the membrane is most likely made good by development of the sphincteric group of muscles and the urogenital diaphragm.

Finally, we may note that the width of the true pelvis is only about one third of that of the abdomen. Consequently, the viscera in the pelvis fill up most of the pelvic floor and separate the peritoneum from the pelvic diaphragm. The viscera really are lying embedded in a mass of connective tissue which forms the various layers of the endopelvic fascia. It is therefore easy to see why hernias through the pelvic floor are rare. The pelvic diaphragm is not a thin muscular layer in contact on its deep aspect with the peritoneum like the anterior abdominal wall. The vagina, in fact, forms the one weak spot in the pelvic floor and it is here alone that we find hernias as cystocele, rectocele and prolapse.

Material used in the preparation of this paper included numerous fetuses from five weeks to term, supplied to me by various members of the Obstetrical and Gynecological staffs of The Royal Victoria Montreal Maternity Hospital, the Jewish General, the Misericorde, and St. Mary's.

Dr. George Corner, Director of Embryology, Carnegie Institute, Baltimore, Maryland, made available to me two sets of stained serial sections of the fetal pelvis, 89 and 112.5 mm. C.R.L.

I am indebted to Professor C. P. Martin for his courtesy in permitting free use of the collection of specimens in Primate Anatomy and also for the great personal assistance he has afforded me.

Dr. S. M. Friedman, Assistant Professor of Anatomy, made several excellent diagrams for me.

May I express my gratitude to those who so kindly placed this material at my disposal.

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In amphibians the recti and puborectalis are in the same straight line, interrupted by the os pubis (Figs. 14, 15, and 16). The recti abdominis and external obliques are attached to the pelvis; their contractions can become efficient only by fixation of this structure. This fixation was primarily attained by the development of the caudopelvic muscles, which thus anchored the pelvis posteriorly. The caudopelvic muscles are relatively of considerable strength, and pass caudally from the pelvis almost in the same straight line as the recti abdominis, and thus are admirably adapted to resist a displacement of the pelvis forwards which contraction of the recti tends to bring about.

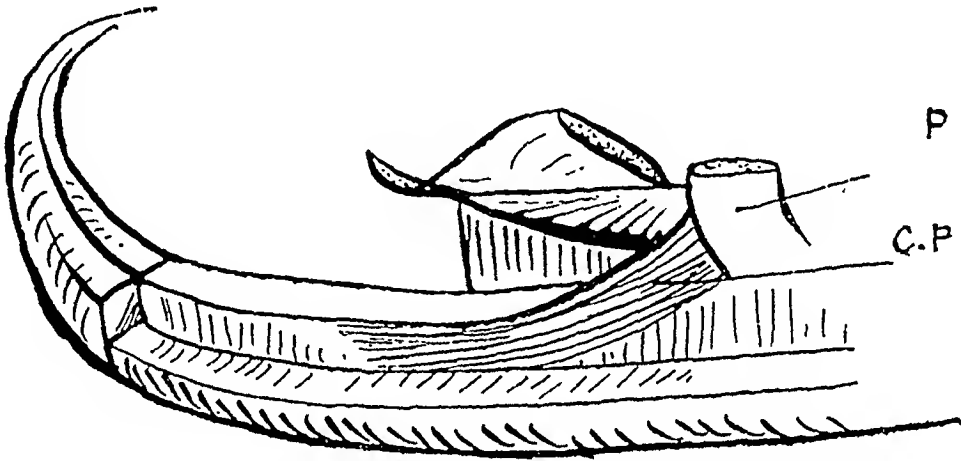


Fig. 14.—Dissection of cloacal region of the dogfish. About one-half life size. P = Pelvic bar bisected and turned outward. C.P. = Caudopelvic strand.

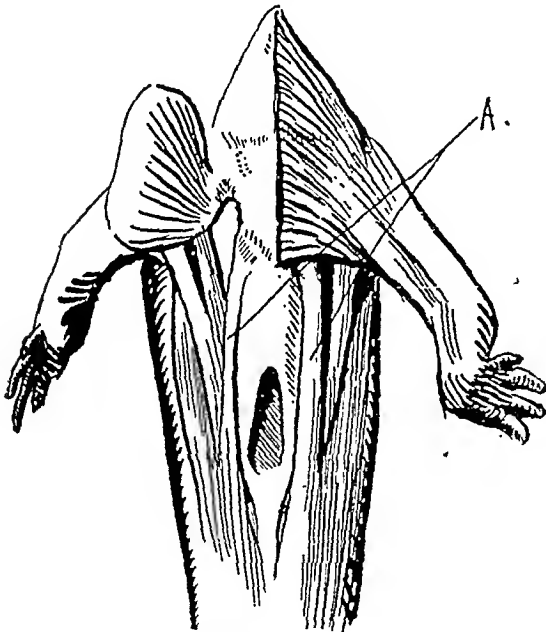


Fig. 15.

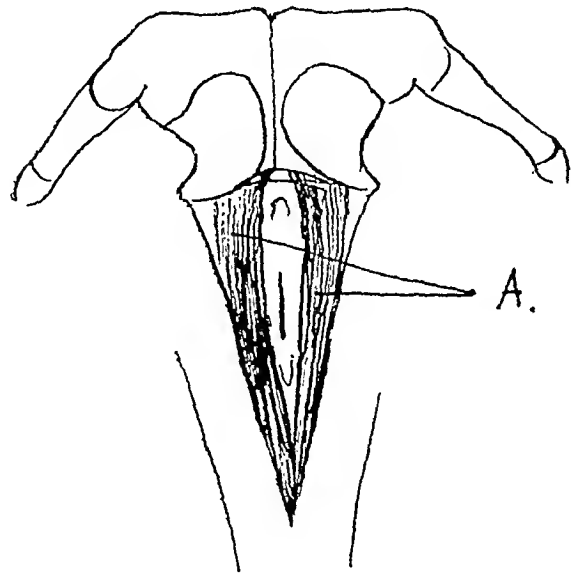


Fig. 16.

Fig. 15.—Dissection of menobranchus showing caudopelvic muscles. A, The cloacal passage has been cut through on a plane with these muscles, and the superficial parts have been removed.

Fig. 16.—Dissection of salamander maculosus to show A, caudopelvic muscles. (After Paramore.)

PLASMA PROTEINS IN PREGNANCY*

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PROTEIN metabolism has been under investigation for nearly one hundred years, but it is only recently that hypoproteinemia has been recognized clinically. The present study was undertaken to determine if a simple method of estimating plasma proteins could be adapted to routine use in office obstetrics, while being sufficiently accurate to be clinically useful. Its application to a group of patients is described and discussed.

A short reference to the physiological and clinical aspects of the plasma proteins will first be made. Much of the evidence in the literature is of a conflicting nature, but certain assumptions appear to be reasonable.

Structure and Function of Plasma Proteins

The plasma proteins include albumin, globulins, and fibrinogen. The albumin fraction is clinically the most important protein in the plasma, maintaining osmotic pressure and viscosity. The globulins take part in antibody formation, and fibrinogen in blood clotting. It is unusual for either to be appreciably lowered in hypoproteinemia, which is always due to a depression of the albumin fraction.^{1, 3-14}

The plasma proteins are maintained either by an adequate intake of protein or when this is lacking, by the so-called reserve stores. These stores cannot be distinguished from the rest of body protein, but participate in the continuing metabolism of the individual. That they are located in the vital organs principally is suggested by the finding that during protein starvation, the liver, kidney, and alimentary tract rapidly give up 30 per cent to 40 per cent of their protein, while that within the muscle remains unchanged.¹⁶ However, as starvation proceeds, plasma¹⁵ and muscle proteins are called on to maintain these organs above their vital levels, and a decrease in the concentration of plasma proteins occurs.

Source of Plasma Proteins.—The plasma proteins are synthesized within the body, from amino acids. The liver is the primary site of formation, but a secondary source, within the reticulo-endothelial system, is suggested to explain the occurrence of nutritional edema, in the presence of a normally functioning liver, adequate intake of protein, and positive nitrogen balance.¹⁷⁻²²

Causes of Hypoproteinemia.—Protein deficiency in the tissues is recognized, almost solely, by a decrease of protein in the blood, with a resulting loss of osmotic pressure. When the albumin fraction falls below 3 Gm. per 100 c.c. edema occurs.¹ Hypoproteinemia may be due to²:

1. *Excessive loss of plasma:* In addition to the plasma loss due to hemorrhage or burns, excessive exudation into the peritoneal cavity, or intestinal walls, occurs in peritonitis, ascites and acute obstruction.

2. *Faulty nutrition:* A lack of sufficient quantity or quality of protein in the diet, or improper absorption of an adequate intake results in hypoproteinemia.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Oct. 27-29, 1946.

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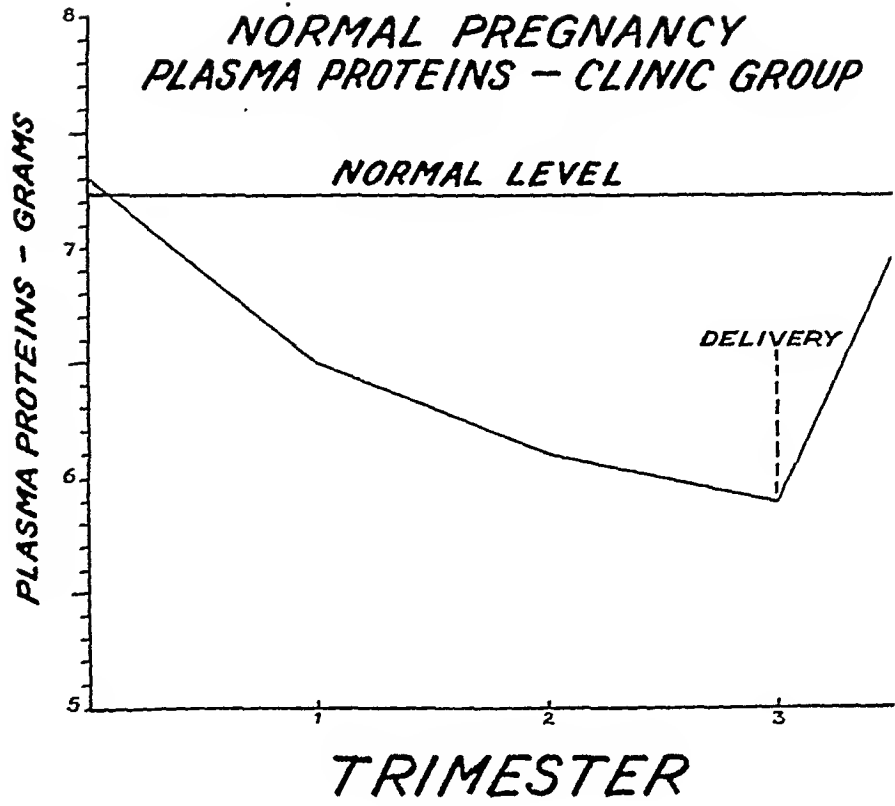


Fig. 1.

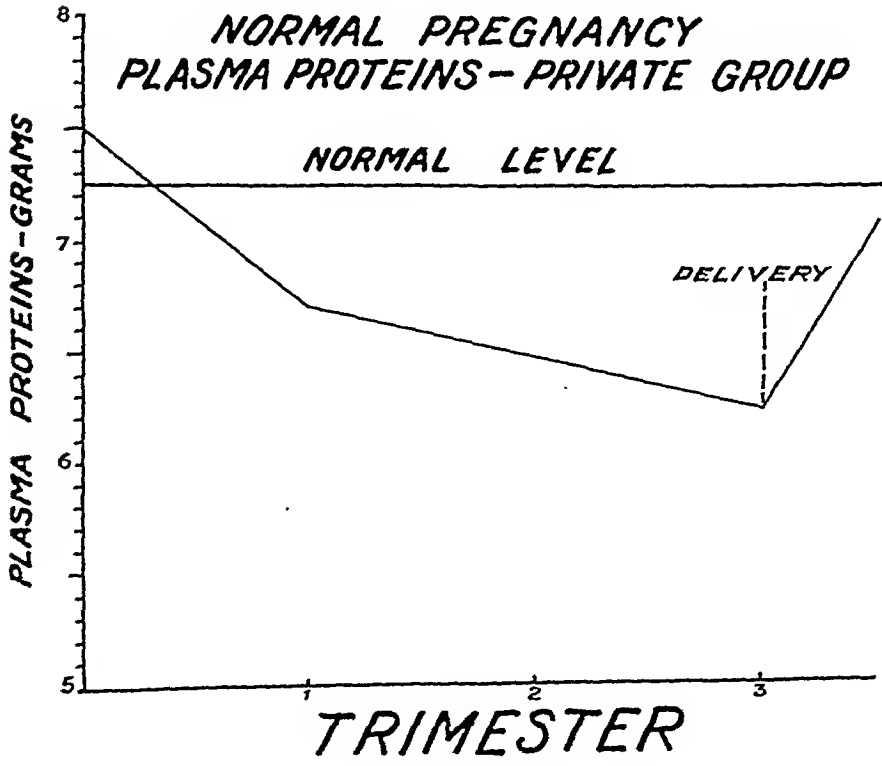


Fig. 2.

3. *Excessive loss of nitrogen:* Operations, various forms of trauma and general anesthesia, cause excessive destruction of protein, and a large amount of nitrogen is lost in the urine. In hyperthyroidism the loss is due to the increase of metabolism.

4. *Defect in synthesis:* Due to its important role in the production of albumin, liver insufficiency is accompanied by severe hypoproteinemia. The defect is not due to faulty nutrition because positive nitrogen balance can be maintained.

Replacement of Plasma Proteins

An adequate intake of biologically valuable protein will prevent hypoproteinemia.^{23, 26} If acute depletion has occurred, diet, intravenous amino acids, protein hydrolysates, or plasma will bring about restoration of normal plasma protein levels if used in sufficient quantities to maintain nitrogen equilibrium.²⁴ When depletion has been of long duration, plasma protein replacement, even with very high intake, may take months.²⁵ In cases of nephrotic and hepatic hypoalbuminemia, the restoration of normal plasma protein levels is notably ineffective.

Until recently, the diet of pregnant women was restricted in its protein content because it was thought to be toxic for the prospective mother. The observation that the patients who ate meat, eggs, and fish seemed to do better led to a study of plasma protein levels.²⁷ Hypoproteinemia was commonly found in pregnancy, and became extreme in toxic patients. It is now generally accepted that high protein intake in pregnancy will appreciably decrease the incidence of toxemia.²⁸

Simplified Method of Estimating Plasma Protein

Measurement of plasma protein concentration by Kjeldahl analysis is a highly technical procedure, and requires elaborate and expensive apparatus. For these reasons it is beyond the reach of the clinician. The use of gravity methods have failed to be satisfactory, until recently, because the organic liquids employed were highly volatile and explosive.²⁹ These difficulties have been overcome by the use of an aqueous solution of copper sulfate, which has a coefficient of thermal expansion almost identical with blood or plasma, and rapid protein coagulating power.

Compared with plasma protein determination by Kjeldahl analysis, the copper sulfate method has proved to be accurate to within ± 0.3 Gm. per 100 c.c.^{29, 30, 31} The stability of the solutions, the rapidity and simplicity of the test, make it ideal as an office procedure.

Blood is withdrawn from the superficial vein of the arm, and allowed to fall into solutions of copper sulfate of known specific gravity. Its behavior after the loss of initial momentum depends entirely upon its specific gravity as compared with the solution into which it has fallen. The ideal anticoagulant for this test has been shown to be heparin.

Application of Test.—The present study has been carried out on a total of 600 normal patients, and a small number with toxemia. The greatest number, totalling 450, were patients attending the prenatal clinic of the Catherine Booth Hospital, but a smaller number were studied in practice on the private maternity ward of the Montreal General Hospital.

Fig. 1 shows the average levels on the group of normal clinic patients. There is a steady fall throughout pregnancy with a rapid rise post partum; although clinically normal, these patients seem to show hypoproteinemia. An almost identical result was obtained with the private patients, even though one would expect a much higher level in this group whose income would allow a more expensive high protein diet (Fig. 2).

each patient. Plasma protein determinations were made at biweekly intervals. Over the three week period, no elevation of the plasma proteins occurred (Fig. 7).

The use of hydrolyzed protein in toxemia has been, of necessity, limited, through the lack of time imposed by the precarious condition of such patients,

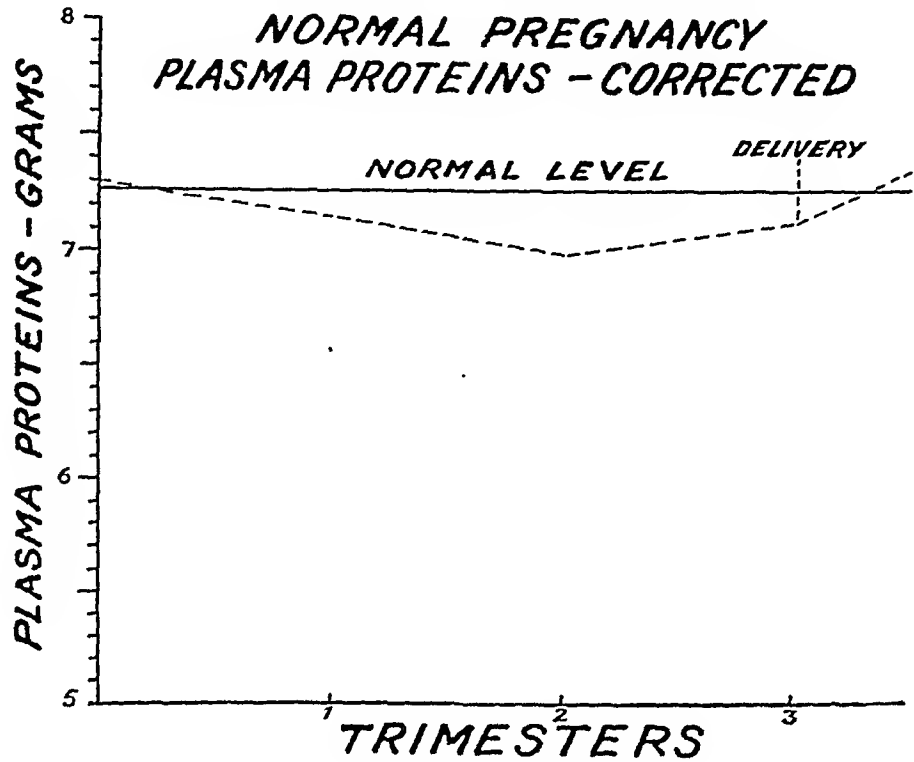


Fig. 4.

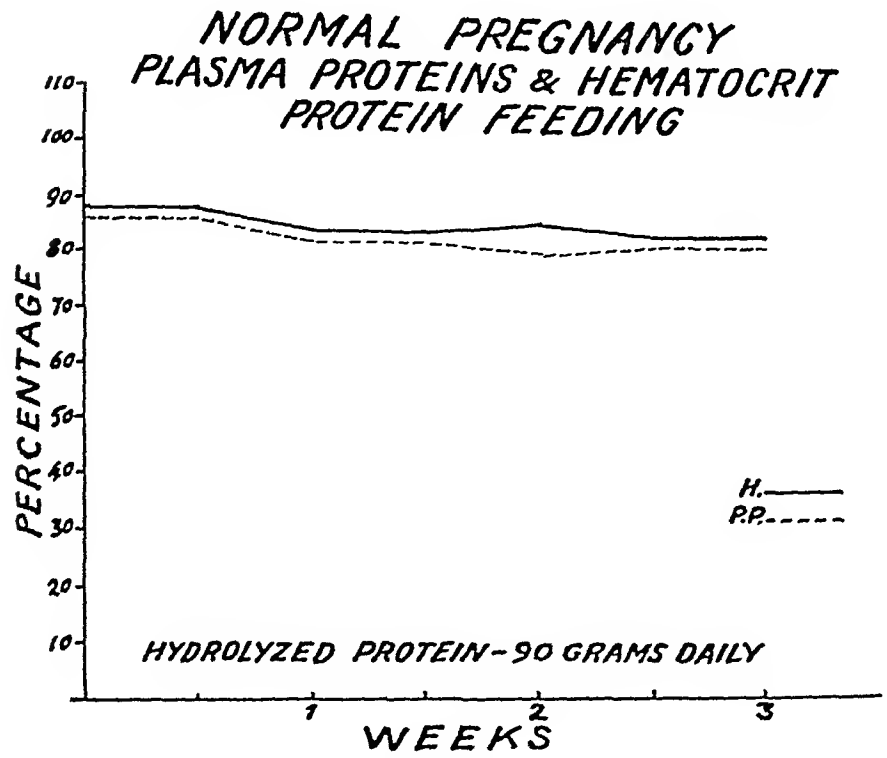


Fig. 5.

The similarity might be explained by the increased hydration of the blood during pregnancy. Hematocrit estimations will reflect changes in blood volume, and can be determined from the specific gravities of blood and plasma.^{32, 33}

When estimated in this manner, they were found to be consistently lower than those obtained by centrifuge, and more accurate as a measurement of the true cell volume within the circulation.³⁴

Protein and hematocrit levels expressed in terms of percentage are practically identical throughout pregnancy (Fig. 3). The hypoproteinemia coincides with the increased plasma volume, and to estimate the true level of plasma proteins the percentage of dilution should be added. Fig. 4, which represents such correction applied to our series of normal patients, shows the plasma proteins well within the normal range.

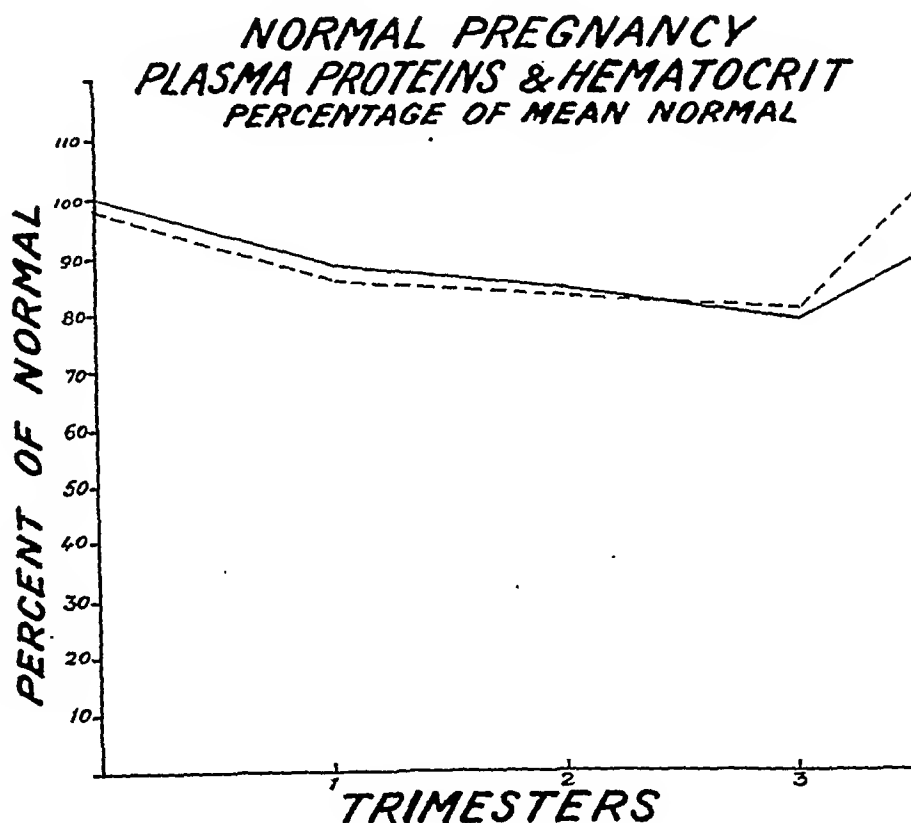


Fig. 3.

After correction for plasma dilution, such normal levels have not been present in the patients with toxemia. Figs. 5 and 6 show a marked difference between the hematocrit and plasma protein levels. In pre-eclampsia, a difference of 30 per cent was found, while in eclampsia the difference became more marked, as the hematocrit levels rose, and the plasma proteins fell. The relationship between hematocrit and protein levels may prove to be a valuable diagnostic aid in toxemias—an increase in difference between them is a poor prognostic sign, while a decrease in difference suggests improvement.

Protein Hydrolysates

During the course of this study, an attempt was made to evaluate the effects of supplementary feedings with protein hydrolysates by mouth and vein, in the normal patients and those with toxemia.

For this purpose, a group of twelve patients attending clinic were fed hydrolyzed protein over a period of three weeks, in the form of an enzymatic digest of casein. A daily supply of 100 Gm. of protein in this form was given

The response to oral hydrolysate supplements prenatally was observed in three cases of pre-eclampsia. In two of them, a daily supplement of 100 Gm. was given over a period of six days, while the third patient was given 200 Gm. daily for four days. No improvement was noted in edema, albuminuria, or plasma protein levels.

Similar observations were recorded when protein hydrolysates were given intravenously. With the preparation used, reactions were common, and included severe vomiting, abdominal pain, and flushing. They appeared when the rate of infusion exceeded $7\frac{1}{2}$ Gm. an hour, or when the preparation was not well diluted. Adequate dosage was difficult because it was necessary to limit fluid intake. Strict routine toxemic care was given simultaneously, so that interpretation of the results was difficult. The record of two patients is included.

One patient entered the hospital with a diagnosis of toxemia of pregnancy. She had gained 12 pounds in weight during a two-week period, with associated edema, and increase in blood pressure from a usual level of 120/70 to 150/100. The urine remained free of albumin. Her plasma proteins on admission were 3.9 Gm. Therapy included bed rest, sedation, a high protein, salt-poor diet, and intravenous protein hydrolysate, totalling 30 Gm. daily. No improvement resulted. Over a period of five days, plasma protein concentration decreased to 3.7 Gm., her weight increased 5 pounds, edema became more noticeable, blood pressure remained unchanged, and her urine output diminished. Premature separation of the placenta and still birth occurred.

Another patient was admitted with eclampsia. Convulsions were frequent, and only partial consciousness was regained between seizures. Her blood pressure was 160/110, almost complete anuria was present, and the albumin content was 10 Gm. per liter. Manifestly, no one should jeopardize the life of such a patient by relying on a measure not proved by clinical trial. Accordingly, morphia and magnesium sulfate were given, and Stroganoff's method of treatment was followed. An intravenous injection of glucose and hydrolyzed protein was administered. Convulsions ceased shortly after treatment was started, and did not recur. A rapid fall in blood pressure, increase in output of urine, and decrease in albumin were noted. Over the next four days, a daily intravenous of 60 to 90 Gm. of protein was given. Reactions were marked but not alarming. The fetal heart sounds disappeared on the second day, and on the fourth day spontaneous labor terminated with the expulsion of a stillborn baby, followed by a prematurely separated placenta. The plasma proteins on admission were 3.98 Gm., and 3.7 Gm. at the time of delivery.

Methionine.—Methionine was administered to a single patient in this study. The patient was admitted to hospital with pre-eclampsia. She had first been seen in February, 1946, and her expected date of confinement was October 3. She was examined at monthly intervals and, previous to Aug. 22, 1946, her weight had increased from 150 to 174 pounds only. Her blood pressure had remained low, around 110/160, and there had been no albumin found in the urine. On this day, Aug. 22, 1946, however, she was found to be very edematous, her weight had increased in one month from 174 to 195 pounds, and the blood pressure was 185/110. The urine contained an abundance of albumin. She had no complaints, and the fetal heart tones were normal. She was admitted to the hospital on the following day, where her weight was recorded at 196 pounds, albumin 4 Gm. per liter, plasma proteins were 4.35 Gm., and blood pressure 180/120. A high protein, salt-poor diet was ordered, along with complete bed rest, phenobarbital twice daily, magnesium sulfate by mouth to induce watery stools, and oral hydrolyzed protein to tolerance.

who usually must have their pregnancy terminated soon after admission to the hospital. In our experience, the plasma proteins rise rapidly post partum in both the normal and toxic patient, and they have not been included.

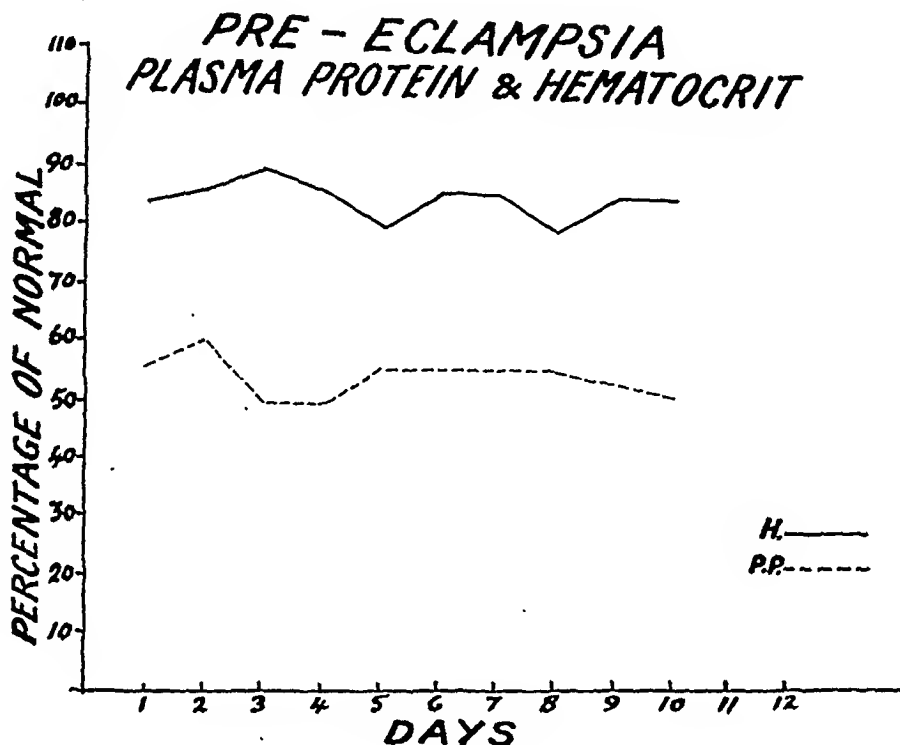


Fig. 6.

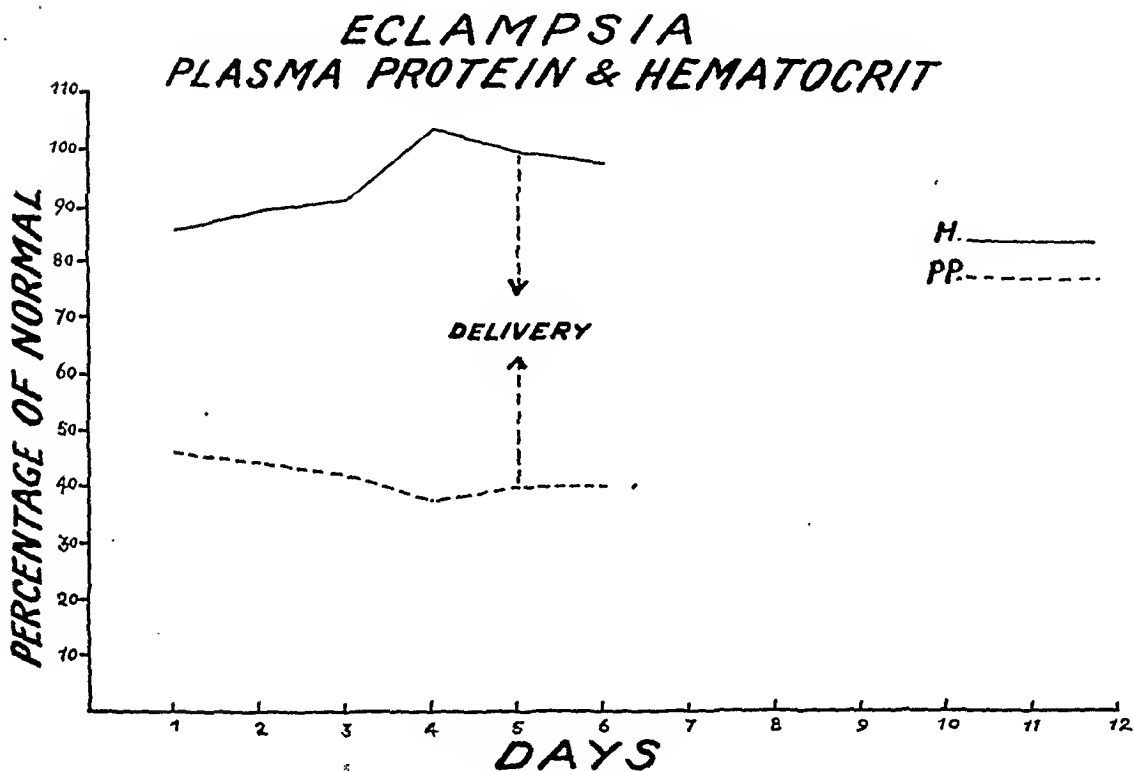


Fig. 7.

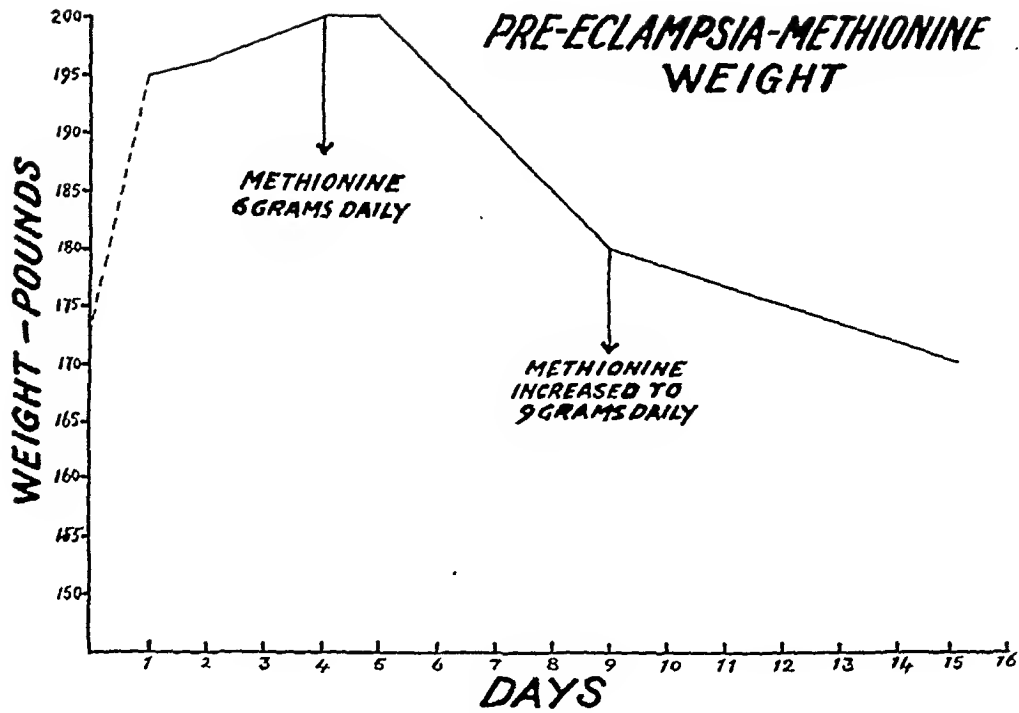


Fig. 10.

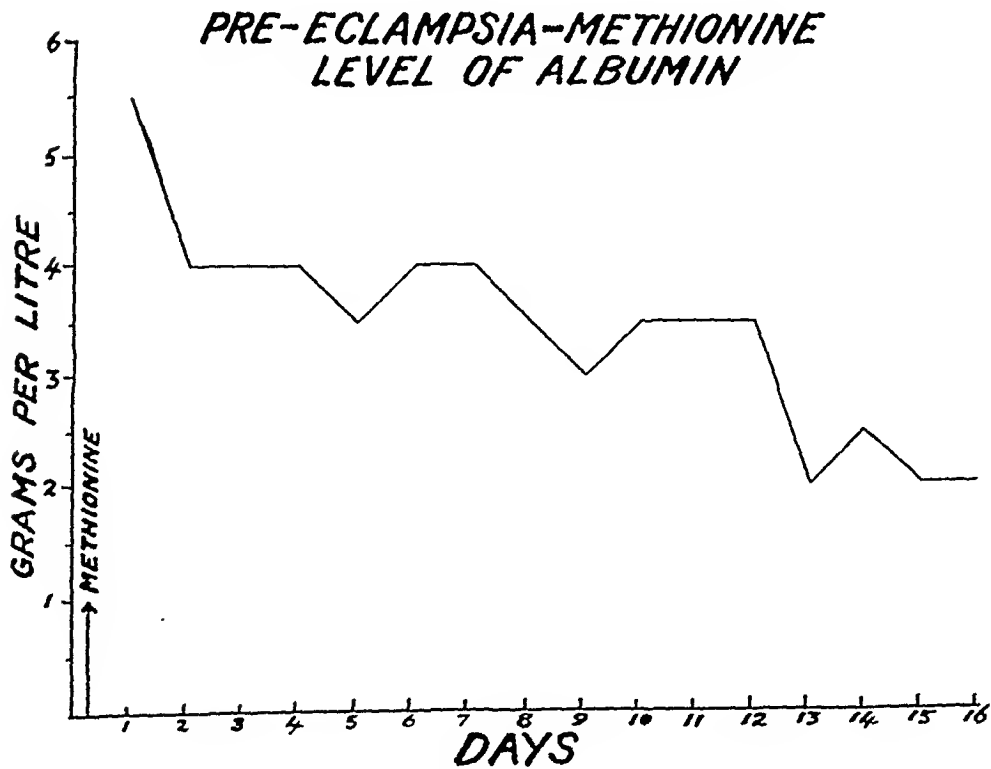


Fig. 11.

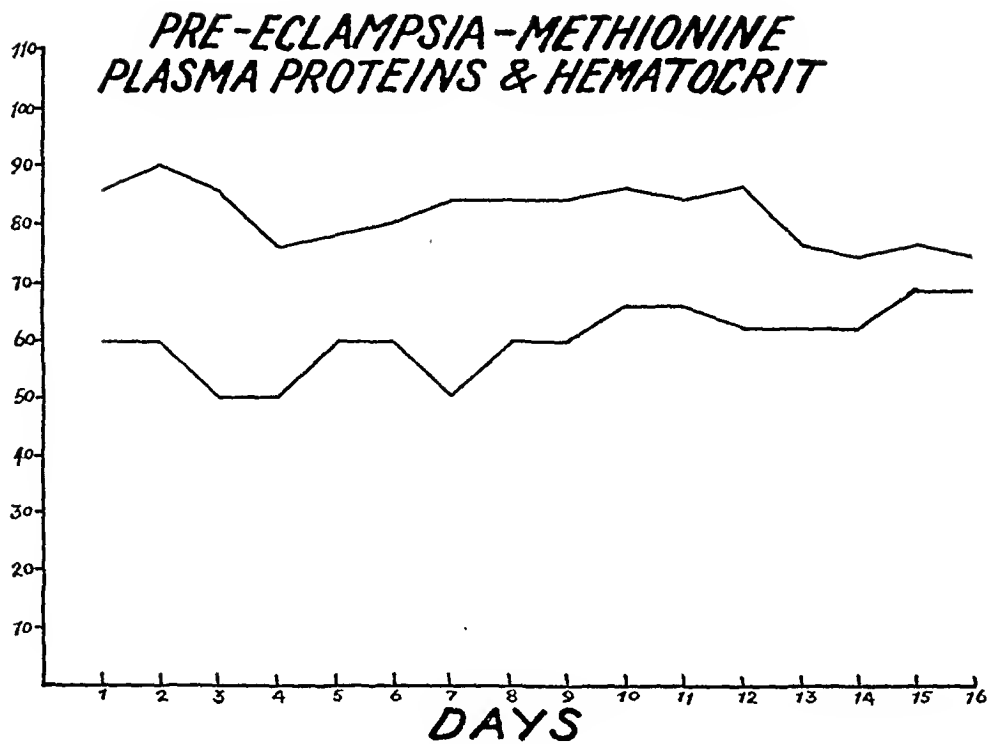


Fig. 8.

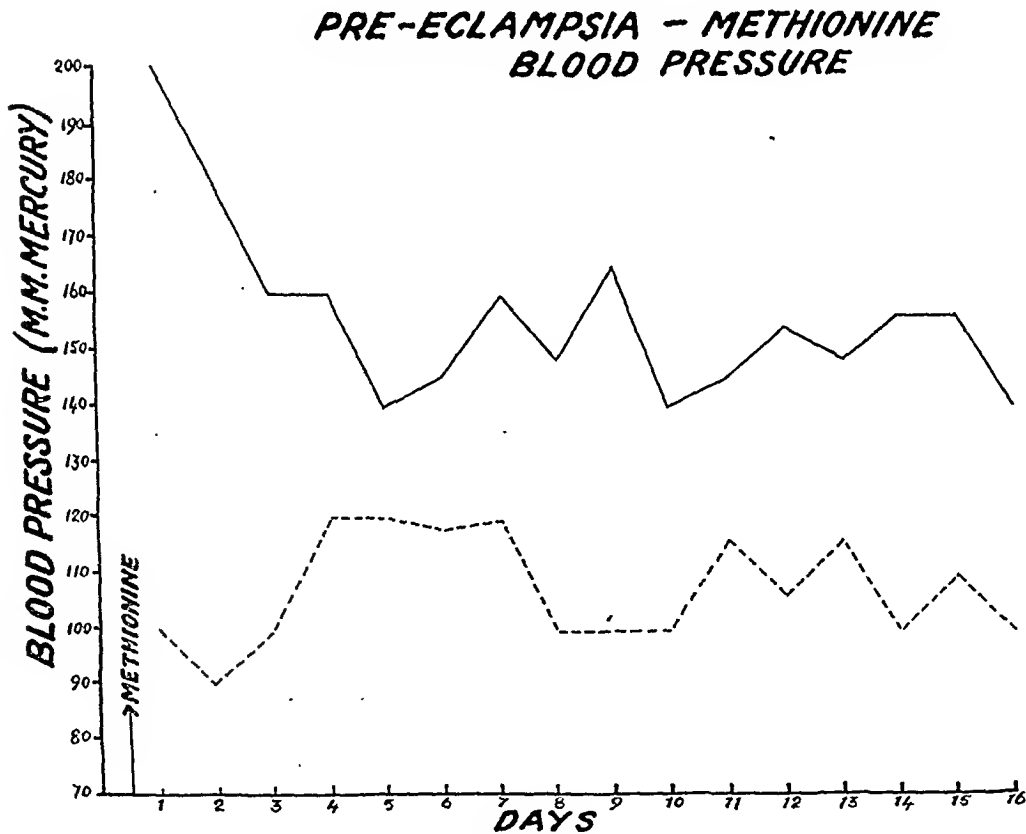


Fig. 9.

Hydrolyzed protein may be administered as a supplement prophylactically, or as a temporary therapy, when digestion or absorption is impaired. Our experiences in this study have left doubt as to the value of such substances in pregnancy. The daily ingestion of large quantities caused no increase in the concentration of plasma proteins over a period of three weeks. It may be assumed that the levels in the normal patients were due to hydration of the blood, the patient was not truly depleted of protein, and therefore added feedings were not necessary. If such an assumption is false, the only other conclusion tenable is that these patients are chronically hypoproteinemic, and prolonged feedings over months would be necessary to increase plasma protein concentration. Hydrolyzed protein is far too expensive to be used in this manner in practice.

No pre-eclamptic patient so treated in this study responded clinically, or had an increase in the concentration of proteins in the plasma before delivery became imperative. Although the patient with eclampsia improved rapidly, she was under strict eclamptic regime with sedatives, and death of the fetus was not prevented.

Methionine is one of the essential amino-acids. It is closely related to cystine and both are sulfur containing. Feedings of cystine-choline or methionine mixtures exert a beneficial change upon a damaged liver.⁴⁰

Liver necrosis, similar to that seen in human eclampsia, can be produced in animals by protein starvation.⁴⁰ Such experimental dietary hepatic injury is often combined with bilateral hemorrhagic cortical necrosis of the kidney, seen in human beings only during pregnancy.⁴¹ Both can be universally prevented by the ingestion of protein with high methionine content such as serum albumin, casein, and egg white.

In rats who had developed ascites on a protein deficient diet, a reversal of the condition was obtained by feeding methionine. The first change observed when such therapy was instituted, was marked diuresis similar to that noted in our case.⁴⁰

In pre-eclampsia and eclampsia, several investigators have studied the function of the liver, and have produced evidence to show that impairment exists.⁴²⁻⁵² The toxic hepatitis produced by carbon tetrachloride and chloroform⁴² has been benefited in both animals and human beings by the administration of methionine.^{53, 54, 55}

Prevention of hepatic injury in human beings requires a daily intake of from 2 to 4 Gm. of methionine or a protein rich diet with a high methionine content.⁴⁰ Limitation of fat is essential since it has been shown to aggravate hepatic injury and to prevent the metabolism of protein.

Although experience with methionine in this study has been limited, the observed dramatic changes in weight, edema, and clinical improvement, after five days on usual pre-eclamptic routine had failed, suggest that the results in animal experiments may be hoped for in human subjects. We chose the oral route of administration because it seemed more likely to concentrate the methionine in the liver by way of the portal circulation. Quicker results appear likely when the substance is used intravenously.⁴¹

Summary

A study of plasma proteins by means of the copper sulfate test upon 600 patients during pregnancy is presented. The effect on plasma protein levels and clinical condition by feedings of protein hydrolysates, and methionine is recorded.

During the following four days no improvement was observed. On August 27 her blood pressure was 200/130, weight 198 pounds, and albumin $5\frac{1}{2}$ Gm. per liter. The fetal heart tones were normal, but the baby was estimated to be less than 4 pounds. The plasma proteins were 4.25 Gm. per 100 c.c. The urinary output averaged 1,000 c.c. daily.

The hydrolyzed protein was discontinued, and methionine was started, with a daily total dose of 6 Gm. being given by mouth. No other change was made in treatment. During the following twenty-four hours marked diuresis began (Fig. 8) and was accompanied by a steady fall in weight (Fig. 9). The blood pressure did not appear to be affected (Fig. 10). The level of albumin steadily decreased during the course of treatment (Fig. 11). Condition of the mother was excellent clinically, and the fetal heart tones remained regular. The day preceding labor her weight was $171\frac{1}{2}$ pounds, a total loss in two and one-half weeks of $26\frac{1}{2}$ pounds; urinary output was 2,540 c.c.; blood pressure average 160/100, and albumin $2\frac{1}{2}$ Gm. per liter. The plasma proteins showed a gradual, although slight rise to over 5 Gm., and approached the hematocrit levels. Labor was normal, and a living $4\frac{3}{4}$ pound baby was delivered.

Methods of Supplying Proteins

The use of protein feeding by mouth should be regarded as of major importance. The use of hydrolyzed or predigested protein, orally and intravenously, is becoming popular. A third method, still largely experimental, is the ingestion of certain amino acid components of protein. Evidence produced in animals supports the hope that methionine especially may be proved to be specific in protecting the liver against the ill-effects of protein starvation, or toxic substances.

The ideal diet in pregnancy must fulfill certain requirements. It must furnish protein in biologically valuable form; it must allow such protein to be used by the body for the optimum construction of the fetus, and replacement of wear and tear tissue in the mother; it must be sufficient to allay hunger; it should, if possible, be acceptable to the patient.

Protein itself, unless protected adequately within the body, will be largely broken down and used as a source of energy. When large amounts are given intravenously, approximately 50 per cent is deaminized and used as a source of calories.³⁵ Several dietary factors conserve nitrogen within the body and prevent such breakdown. If protein intake is high, a sufficient portion will be spared to supply the patient's needs, but, being expensive, cannot be taken in such quantities by the less fortunate group of patients. Furthermore, excessively high protein diets are not well tolerated by many people.

Protein of high biologic value, such as meat, milk, and eggs, is more readily retained. In this sense, vegetable protein is a sparing substance, too, in that it will be deaminized by the body before the more valuable animal protein. This "protein protection of protein" probably explains the good health maintained by people who live on the so-called vegetarian diet.

A third and very important factor is the protein sparing value of carbohydrates, which enhance the storage of nitrogen within the body.³⁶ Furthermore, the time of ingestion of carbohydrates must be emphasized, for they exert their greatest protein-sparing action only when they are available during the period that the intensity of protein metabolism is at its maximum.^{37, 38, 39} This interval is limited to within four hours of ingestion of the regular meal.

Positive nitrogen balance can be maintained by the use of a high carbohydrate, low fat, high protein diet, even with low caloric intake, by the simple maneuver of saving 20 Gm. of carbohydrate from each of the three main meals, and feeding this portion in the midmorning, midafternoon, and evening.³⁷ There is relief from midmeal hunger, and the decreased physical efficiency seen when the stomach is empty.

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Discussion

DR. CANNELL.—Dr. Macarthur has presented results of a very interesting and careful study of plasma proteins in 600 patients. His findings are corroborated in general by many other investigators. To me the principal value of his work is that he has drawn our attention to a simple and accurate method of estimating plasma protein which he tells me, and other biochemists have told me, is quite capable of use as an office procedure. Dr. Macarthur has shown by his paper that this procedure is a useful one which can be adapted to office practice. I feel that anything which will add to our accurate treatment of patients during pregnancy is something that should be drawn to general attention, and he has done that.

From his paper I was not clear whether the relationship between the hematocrit and plasma protein levels preceded the clinical changes which we know as pre-eclampsia, i.e., elevation of pressure, edema, and the other signs. I hope that Dr. Macarthur will clear this up for us. If these findings are found to precede clinical signs by any appreciable time, it is a much more valuable procedure than just an aid in the dietary care of a patient.

He stated earlier that the changes in the liver which are produced by protein starvation are the same or similar to those encountered in the patient dying from eclampsia. I cannot agree that there is any typical picture of eclampsia in a large series of cases. I think that probably about 50 per cent is the maximum number of patients who will show the changes in the liver said to be typical of eclampsia. He has told me that he does not feel that that is of importance in any case, because he is not trying to advance a theory for the cause of eclampsia, but noted that in patients who had a poor protein intake these changes could be induced more readily.

In conclusion, I would like to congratulate Dr. Macarthur on a very excellent presentation, and would urge him to proceed with his studies, particularly with respect to methionine, as it is very interesting.

DR. VAN WYCK.—I believe that thirty years ago it was pointed out that in analyzing the behavior of the serum protein fractions in pregnancy, the shift in the relationship of albumin and globulin was very marked in the toxemias. This was a diagnostic point in the differentiation of eclamptic toxemia from other forms of renal disease in pregnancy. Some years ago Harding noted that in early pregnancy, when the ovum is acting to some extent as a parasite, there was a fall in the serum protein due to the physiologic hydremia,

Conclusions

1. The copper sulfate method for measuring the specific gravity of the blood serum or plasma gives satisfactory and clinically accurate estimations of plasma protein concentrations. It is simple, quick, and may readily be carried out as an office procedure.

2. Combined hematocrit and plasma protein estimations give more information than the plasma proteins alone.

3. The hypoproteinemia of normal pregnancy is relative to plasma dilution.

4. Over short periods of time, feeding of hydrolyzed protein by mouth or vein produces no elevation of plasma proteins, or improvement in the clinical condition of patients with toxemia of pregnancy.

5. The hypoproteinemia of pre-eclampsia and eclampsia is very likely due to failure of albumin synthesis by a damaged liver.

6. The essential amino acid-methionine, may, by its protective action upon the liver, materially aid in the prevention and treatment of toxemias of pregnancy. Further experience with its use is necessary.

I would like to express my appreciation to Drs. Paul Guorgy, A. D. Campbell, N. W. Philpott, and J. S. L. Brown for their criticism and help. The oral hydrolysate used was supplied by Frank W. Horner, Inc., the intravenous hydrolysate by Frederiek Stearns & Co., and the methionine by Ayerst, McKenna, and Harrison.

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A STUDY OF MATERNAL MORTALITY IN CANADA*

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DURING the last ten years the maternal death rate for Canada has shown an encouraging improvement. In 1934 the rate was 5.3; 1936 to 1940, 4.6; 1941, 3.5; 1942, 3.0; 1943, 2.8; and 1944, 2.7. We owe this steady improvement to several factors, such as better hospital facilities and the increased desire on the part of patients to seek hospitalization, improved obstetric technique, and the many prenatal services now available, with the education of the lay public of their value. The use of blood and plasma, the sulfonamides, and penicillin have all contributed to the reduction of maternal mortality. The improved methods of anesthesia and the more efficient methods of relieving the pain of labor have also reduced the number of fatalities.

In 1934 there was a range in the maternal mortality rates for the provinces from 4.1 to 2.3, and in the rates for larger cities of 40,000 population and over, from 5.9 to 1.0. The range in 1940 for the provinces was from 4.8 to 2.9, and for cities of 40,000 population and over, 7.0 to 2.1.

In the study of statistics of the past ten years, the chief causes of death of puerperal women are infection, toxemia, and hemorrhage, and in the order stated. In 1939, 72.6 per cent of all maternal deaths were due to these causes: septicemia, 32.1 per cent; toxemia, 24 per cent; and hemorrhage, 16.5 per cent. In 1934 401 women died of septicemia and septic abortion. In 1944 there were 265 women who died from these causes. Although there has been this marked decrease in the number of deaths from sepsis, it still remains the most frequent cause of maternal mortality.

Many of these deaths may be deemed preventable, and the prevention is chiefly the responsibility of the physician. The causes of puerperal sepsis are found to be prolonged labor, anemia, or blood loss, cesarean section, and operative obstetrics. Prevention is accomplished only by good obstetrics. Deaths from septic abortions, of which there were 85 in 1944, are included. These cases are a problem unrelated to maternity for which the profession is seldom directly responsible. The medical profession, however, should lead the way in finding a means of preventing these deaths from septic abortion.

In 1934 toxemia, the second greatest cause of maternal mortality, was responsible for the loss of 260 mothers.

In 1940 mortalities from this cause numbered 234, or 23.9 per cent. In 1941 toxemia was the largest single cause of maternal deaths accounting for 222, or 24.7 per cent. In 1942 the rate was 22 per cent; 1943, 20.3 per cent; and in 1944 it had fallen to 15.7 per cent.

*Presented at the Second Annual meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

but that when the patient developed hyperemesis gravidarum, the serum proteins were concentrated, the total figures rising sometimes to 9 per cent, this rise being the measure of acute dehydration. With prompt treatment in an attempt to restore the water balance, the serum protein figures fell back below the prepregnant level as the patient recovered. Harding pointed out, however, that closely recurring attacks of dehydration produced a destruction of these blood substances due to the effort the body made in the contracted and concentrated blood volume to restore the changed viscosity. At first a rapid rise in serum protein followed by a fall and then a rise with a further attack of dehydration, and then a recurrent repetition of this phenomenon ultimately resulted in a low fixed blood protein. Harding regarded this ultimate fixation of the serum protein as a bad prognostic finding. The strange behavior of plasma proteins in pregnancy is now the subject of much investigation, and promises much in the understanding and therapy of toxemia.

DR. EDWIN ROBERTSON.—The point which I should like to hear discussed is one which has not already been mentioned, namely, the specific nature of the toxemia of pregnancy. I am referring to the work of the Smiths in Boston who, some time ago, discovered a toxic factor. The Smiths thought it possible that there must be something in the folklore which points to menstrual discharge being poisonous; they found a highly toxic pseudoglobulin in menstrual discharge similar to that which Menkin had isolated in turpentine-produced pleural effusion in dogs. They also found such a toxic factor in the blood of women suffering from toxemia.

I wonder whether, in his study of toxemia, Dr. Macarthur has taken cognizance of the Smiths' work on the subject.

DR. PHILPOTT.—I believe that perhaps the most important contribution that will be made in the treatment of toxemia and eclampsia might be in this direction. We do not know much about the causation of toxemia today, but we struggle with many causes. There is a very definite relationship between toxemia and low plasma protein. We have had in the last two years several cases that have responded very well to different forms of supplementary protein administration. One case under study had a very low plasma protein, 3 Gm. per cent, and was treated with plasma transfusion. Three transfusions of 250 c.c. each were given in four days. At the time of her first transfusion blood pressure was 200, eyes were almost closed with edema, and the patient looked as though she were head for a convulsion. With the first transfusion the symptoms started to disappear, and with the third she was normal with reference to the edema and blood pressure. The patient was carried along for some time and she was delivered a few weeks later of a normal baby. She showed no sign of toxemia at the time of delivery.

I believe there is a great future with Methionine. It is used in our clinic for post-operative cases in shock and has been managed by Dr. Browne with excellent results. We find it a most beneficial way of treating cases of suspected or definite liver damage.

DR. MACARTHUR (Closing).—In reply to Dr. Cannell, I must say that we have as yet not established the value of the hematocrit-plasma protein test in the early, sub-clinical, toxic woman. The source of my impression regarding hypoproteinemia is mainly the work of Gnorgy, who has shown that prolonged protein starvation in animals causes necrosis of the liver identical to that found in human eclampsies, often combined with bilateral cortical necrosis of the kidney.

We have not used plasma in the treatment of toxemia, chiefly because it is difficult to obtain, and protein hydrolysates are much cheaper, although perhaps not as physiologic.

I freely admit, with Dr. Robertson, that many interesting hormonal theories have been elaborated, to explain pre-eclampsia and eclampsia. Liver damage may not explain this complex disease, but may be an important link in the chain. Perhaps by its adequate protection we may go far in finding the solution.

I would refer Dr. Puddicobe to the articles of Phillips and others in which they give the complete technical details of plasma protein, serum protein, hematocrit and hemoglobin, and red cell counts. Their directions are sufficient to enable anyone to carry out this test in the office.

If excessive blood is lost, it should be replaced as soon as possible and in sufficiently large amounts. Blood is the puerperal woman's most powerful ally but if not immediately available, plasma is now procurable in even all outlying districts. We have become aware of its lifesaving qualities in cases of shock, yet more and more it becomes apparent that plasma will not save life if the blood loss has been great. Some method whereby hospitals can get blood replacement easily, cheaply, and promptly is very important. If veins cannot be entered, bone marrow infusion through the sternum is a procedure which should be used.

According to the statistics of the Chicago Lying-in Hospital, heart disease has been one of the major causes of maternal death. Our Canadian statistics of maternal death do not list death from cardiac disease. The rate of mortality from phlegmasia alba dolens, embolism, or sudden death does not run a parallel course with sepsis. An almost steady rise occurred since 1934, ending with a definite peak in 1940 with 156 deaths. The rates for all other conditions except accidents were the lowest in that year. The rate in 1944, however, was the lowest ever recorded—seventy-six deaths.

Under the heading of other accidents of childbirth are included cesarean operations, other surgical operations, instrumental deliveries, dystocias, ruptures of the uterus in parturition, together with other or unspecified conditions of the puerperal state, as puerperal diseases of the breast, etc. In 1940, ninety-nine deaths were attributed to these causes, which was 8.3 per cent. Since 1936 there has been a steady decrease in these numbers. The use of blood and plasma has decreased the number of fatalities from cesarean section. The careful selection of cases, improved preparation, better methods of anesthesia, and the lower uterine segment type of operation has made it a safer procedure.

The prevention of maternal mortality should begin in childhood. In the prevention of rickets, tuberculosis, syphilis, and the acute communicable diseases of childhood, we are laying the foundations for a healthier motherhood. The growth and normal development of girls are dependent largely upon proper nutrition, freedom from infections, and suitable exercise. It is well known that rachitic pelvises, damaged hearts and kidneys, and chronic foci of infection increase the risks of pregnancy. Health should be regarded as a major objective of modern education. In all secondary schools ample provision should be made for mothercraft classes to be instructed by well-trained and experienced public health nurses. These should be made compulsory for all girls. They would be better equipped for motherhood, would also have a fund of knowledge which would help them to meet the broader problems of social hygiene. Another important factor in the reduction of maternal mortality is the puerperal woman herself. The ability to choose a skillful physician, a competent nurse, and a well-equipped hospital are of vital importance. Her capacity to grasp and to carry out simple hygienic rules and her "teachability" as to the importance of symptoms and signs, which indicate approaching danger, are large factors.

A well worked-out program of parental education should be available in every community in which parent-teacher associations, women's clubs, etc., should be encouraged to take an active part. Prospective mothers of all grades of

The promise of still greater improvement will depend upon close supervision of all pregnant women, and the earliest possible recognition of the actual appearance of toxemia. The causes of the toxemia of pregnancy are still unknown, and the prophylaxis is still better than cure. Good prenatal care, increased hospitalization of pregnant women, and prompt institution of bed-rest treatment of even the mildest case of toxemia will give us improvement. Prevention of the occurrence of eclampsia in a noneconvulsive toxemic patient by proper medical management is of paramount importance. The mortality of the convulsive toxemias is eighty times as great as the noneconvulsives.

The accuracy and value of statistical deduction depend upon the quality of the information furnished by the certificate of death. The figures for 1941 to 1944 were compiled according to the fifth revision of the *International List of Causes of Death* and are not strictly comparable with the figures for 1940 for individual causes. Obstetric death is commonly the result of several causes, rarely one, and actually it is very often impossible to assign death to one cause.

It has been said for many years that infection as the most common cause of maternal death is the most important. Hemorrhage is no doubt far more common everywhere than indicated by its statistical frequency, and it is the outstanding controllable factor. Preventive measures for reduction in maternal mortality will produce greater results if we place emphasis on hemorrhage rather than infection. At present hemorrhage is the most important cause of maternal mortality, and probably the most common as well. In a study of the Maternal mortality statistics of the United States for 1941 and 1942, it was found that in 1942 there was a 10 per cent reduction in the deaths due to infection, an 11 per cent reduction in deaths from toxemia, but practically no decrease in the number of deaths from hemorrhage. In Canada there has been little, if any, improvement in maternal mortality from hemorrhage since 1931, when there were 137 deaths from hemorrhage. In 1940, maternal deaths from hemorrhage numbered 138, comprising 14.1 per cent of all maternal deaths. In 1942 there were 155, comprising 17.2 per cent. In 1943 there were 170 deaths from hemorrhage. In fact, hemorrhage was the largest single cause of maternal mortality, 21.3 per cent.

Undue loss of blood is to a great extent preventable. Hospitalization of every woman who bleeds during her pregnancy, and routine blood studies with blood typing and the determination of the Rh factor are essential. Many of the obstetric complications are influenced by hemorrhage. In the early months of pregnancy ectopic gestation and abortions are the chief causes. Later in pregnancy placenta previa and abruptio placentae cause the serious hemorrhages. In the delivery, trauma and the placental stage are the main causes of death from hemorrhage.

Proper conduct of the second stage of labor and conservative management of the third stage will reduce materially the deaths which are directly due to hemorrhage, and will also enable the puerperal woman to combat complications, particularly infection and toxemia, which might otherwise prove fatal.

DR. HECTOR SANCHE.—This ten-year analysis of maternal mortality in Canada is of pre-eminent interest, and the steady improvement it has shown, improvement which goes on in 1945, whose maternal death rate has been 2.3, is an encouragement to the medical profession.

Although there is a considerable improvement as a whole, each of the eleven headings under which deaths from puerperal causes are classified do not mark great percentage changes in regard to the total.

The three chief causes of maternal deaths are always septicemia, toxemia, and hemorrhage, and in the order stated; they stand for 70 to 75 per cent of all deaths. Septicemia has kept approximately its same percentage, toxemia has improved, while hemorrhage has increased.

Dr. Kerr has stated as factors of improvement: better hospital facilities, increased desire on the part of patients to seek hospitalization, improved obstetric technique, prenatal services, use of plasma, sulfonamides and penicillin, and has emphasized the development of these factors to a higher level.

Three parties are interested in the improvement of the maternal death rate: the medical profession, the patient, and the public. All three must cooperate if we want to get better results.

I can say that the medical profession as a whole is always looking for better standards in medical care. But we cannot bring for comparison specialists who work in favorable conditions, who are ready and able to improve their obstetric technique, and the general practitioner.

All hospitals will tell us that their maternal death rate is brought higher than it should be, not from their booked cases, but from their emergency cases. What does this mean? That the medical care is not of the same standard inside and abroad. And why? Because the factors mentioned above are not found at the same level here and there.

If we want to keep on the downward grade of the maternal death rate, we must continue the work in hospitals, but we must also help the general practitioner and enable him to share the benefit of our work, both in researches and facilities.

Most of us are teachers in our different communities, and we are aware of what our students know when they leave the University. They are well enough equipped to look after normal obstetric cases, but how many eclamptic patients have they seen, how can they handle a case of dystocia? And I would add, when will they be able to handle these properly if we admit that they attend fifty to sixty maternity cases a year, and when we know that severe dystocia or pathologic cases are sent to a far-off hospital where they cannot be associated with the delivery, and perhaps hear about the treatment only by the patient's own report.

The patient's cooperation consists in having her come to the doctor's office or to the clinic for medical supervision first, and second, in having her convinced of the importance of the directions she is given.

The increased desire on the part of patients to seek hospitalization is actually entailed by the hospital facilities. Live births in institutions have increased from 39 to 60.9 between 1938 and 1944, and this increased demand has created shortage of hospital beds. On the other hand, when birth in an institution is mentioned, "institution" does not necessarily mean a well-equipped hospital.

We should also bear in mind that 90 of 798 mothers died in 1943 without having a doctor in attendance, that is 11.3 per cent. This fact may come from two causes: (a) neglect on the part of the patient, (b) scarcity of doctors.

The cooperation on the part of the second party will be obtained inasmuch as the third party, the public, is aware that pregnancy is a matter that should be prepared and looked after, and that it is now recognized that prenatal hygiene, prophylaxis, and medical attendance will save many mothers' lives.

And here I agree with Dr. Kerr's recommendations that the prevention of maternal mortality should begin in childhood, that parental education, and that the education of the public should be done through the press, radio, and all other possible media.

intelligence and of all social classes will take advantage of instruction for expectant mothers, if presented by thoroughly trained and experienced public health nurses.

This instruction should be made available to all prospective mothers and fathers, regardless of their economic condition.

If 85 per cent of the maternal deaths are preventable as one obstetric authority states, the time is ripe for action. Judging by accomplishment in other fields, a "*Canadian Safe Motherhood Association*" or some such name would serve to crystallize the energy awaiting leadership. Obstetric authorities are prepared to give expert advice; public health workers are accustomed to organize and promote, and the informed public will furnish the financial support.

Medical and hospital care should be supplemented by education of the public, through the work of public health nurses, the press, radio, and other media, regarding the need for, and value of, good maternity care. The public should be instructed as to the proper diet and hygiene for the mother during the maternity cycle. There can be no question that well-equipped maternity hospitals with skilled staffs, using conservative methods of treatment, are the safest places in which to have a baby. In Canada, one of our great needs is increased hospital accommodation. It is estimated that only 47 per cent of pregnant women in Canada are able to be delivered in hospitals. To assure maintenance of adequate hospital maternity services in any community, hospitals must not be dependent upon charity contributions and upon the extra charges of private patients to meet the loss through its free services. Any approved hospital should be supported from public funds on a cost basis for providing all in-patients maternity care, the cost of maintenance of facilities for the prenatal care and all laboratory and x-ray services. The maternity patient administration is a community responsibility, and a larger provision should be made from public funds.

We do want to have the best maternity care for all mothers that it is possible to provide, so that Canada will be a place of safe motherhood.

Discussion

DR. PHILPOTT, Montreal.—Dr. Kerr has shown very ably today that hemorrhage is the greatest killer, and that it is preventable. We shall prevent it only by comparing results in various clinics. I would like to exchange statistics with Toronto, Winnipeg, and Vancouver. We could learn a great deal.

I am sure that in our clinic (Victoria Hospital of Montreal) today half of our patients who die could have been saved had they had adequate treatment. In a society such as this we could go forward in a concentrated effort to organize the management of obstetric patients. We should have some system and recommendations to offer to general practitioners and the public whereby each individual doctor will fit into his proper place. I think, as Dr. Sanchez said, that many general practitioners do not have the right facilities, and specialists are at a disadvantage in having to handle patients that are tragedies before they see them. A plan whereby general practitioners would handle certain types of cases, others to be handled by specialists, and still others handled in hospitals would be advisable. It is the obligation of this society to make this endeavor.

work, giving a clear picture of the types of cases dealt with, the treatment given, and the end results. In addition, it would be of the greatest value if each year a report could be attached giving the particulars of diagnosis and treatment in some special group of cases over the previous five years. For example, this year a survey would be made of results in the management of all types of toxemia, next year possibly hemorrhage could be dealt with. In such a way over a period of years there could be available a vast amount of information pertaining to the treatment of all of the important complications of childbirth in Canada. Such information is not yet available in the literature, and so, if we in Canada could initiate such a plan, real progress would be made.

DR. VAN WYCK, Toronto.—The steadily falling maternal mortality rate in our country is a matter of great gratification. There are really three causes of maternal mortality—ignorance, poverty, and neglect. Poverty we can do little about. Neglect rarely plays a part. Ignorance applies not only to the profession, but to the patient. It is fitting that a society of this kind should undertake a program to consider maternal mortality, but the examination of large masses of statistics, while they have value, are not as important as careful analysis of individual tragedies. There are places in the United States where each maternal death is subject to scrutiny by a committee. It would be well to have committees set up locally and subject these individual tragedies to analysis. The ultimate solution is the education of the profession. This should be done, not in a critical manner, but with a view to clearing up the ignorance of both profession and patient. I believe that this society by a Maternal Welfare Committee could advise the proper authorities in this matter, and that such guidance would be a great step forward.

DR. KERR (Closing).—From Dr. Van Wyck's discussion it would be a very splendid thing if this organization would set up a committee on maternal mortality. It is done in various cities in the U. S. where committees study all maternal deaths.

Well-equipped maternity hospitals with a skilled staff is surely the safest place to have a baby. These hospitals should be disseminated on a larger scale in different centers throughout the country, so that one of them be within easy reach of every practitioner. There the isolated medical man in the country could take his patient to get treatment, if necessary, or to seek advice from a skilled specialist for further treatment at home, without having to lose days of his own time.

Before closing this discussion, I would like to set forth an idea. It is timely to discuss maternal mortality. It has been said that 85 per cent of maternal deaths are preventable; I agree, and they would be prevented if—but there will always be so many ifs—that, it is my opinion, the maternal mortality rate is not likely to come down a great deal more. This is no reason to give up in despair.

But it would be of paramount importance to take more interest in maternal morbidity (morbidity during the puerperium) and permanent invalidity to any degree. So many mothers are crippled, I dare say, to a certain extent after one or several pregnancies. Would it be possible to have a uniform base of obstetric morbidity all over the country, to establish statistics in this regard? In this way we could see the end results of our obstetric work, not only inasmuch as those who die, but inasmuch as they live and go through pregnancies curtailed in health, in their vitality, and in their potential in regard to themselves, their family, and the nation.

And I believe that this society comprised of obstetricians and gynecologists is the organization that should set forth this idea throughout Canada.

DR. FRASER.—There are one or two points I would like to bring up. Dr. Kerr has very ably presented the picture as it exists in Canada and elsewhere. I have always had the feeling that one of the greatest weaknesses of our present system lies in our failure to provide the average pregnant woman with the same type of treatment and care that we give the prospective surgical patient. Over the years there has been developed widely a place for the preparation of a woman for operation. Nothing is considered extravagant in the way of examination of treatment prior to the event, yet the average pregnant woman who is about to undergo a surgical procedure receives very scanty consideration. Often a woman approaches delivery with a hemoglobin of 50 to 60 per cent—sometimes less, far below the level considered necessary for a surgical operation. It is possible and should be regarded as essential that the hemoglobin level in pregnancy be maintained at or near 100 per cent. *What then is required is the provision for each and every pregnant woman of a sound and complete medical examination?*

In the report of the *British Committee on Maternal Mortality* tabled in the House of Commons in 1932, in which a very large series of Maternal deaths were analyzed, it was possible to recognize two large groups of cases: (1) those where death was due to childbirth, directly; (2) those where death was indirectly due to childbirth. In group 1 sepsis played a leading role. It was shown that the occurrence of sepsis over the previous hundred years displayed about the same incidence. Reports from Ottawa show the high incidence of sepsis in the causation of death from childbirth. I wonder if we are convinced of the importance of nasopharyngeal infection (active or latent) in those in attendance on pregnant women? Colebrook and his group in London have shown clearly the possibility of transmission of infection from this source and, indeed, have been able to trace the source of infection in many cases to this region. *Sporadic outbreaks* of infection in maternity hospitals may in this way be explained. It is essential that women be delivered in an environment free of infection. Masks should be worn by all those in attendance, and it is possible that some of us by reason of chronic nasal infection may not be able to undertake this special work.

A Final Suggestion.—We have learned much from the preparation of five-year reports on the results of examination, classification, and treatment of cancer of the uterus, particularly the cervix. By study of individual cases, methods of diagnosis and treatment, and as the result of comparison with the results of other observers, progress of a sound type has occurred. I would therefore suggest that a similar procedure be adopted in obstetrics: each hospital where deliveries take place should annually prepare a statement of the year's

Seventh.—The broad and round ligaments, which in their usual position admittedly have little or no supportive action, but which after vaginal hysterectomy, may be employed as a very real support both for the bladder and the vaginal vault.

Uterine prolapse and cystocele following childbirth are the results of stretching or tearing, or both, of the endopelvic fascial diaphragm, and the smooth muscle diaphragm, from their attachments to the uterus and bladder. In cystocele, the pubocervical segments of these diaphragms beneath the bladder may be split in the midline between cervix and pubis. The degree of herniation and prolapse depends upon the extent of the injury, the position and weight of the uterus, and varying degrees of intra-abdominal pressure, but it is facilitated by stretching or tearing of the muscular levator diaphragm which in turn enlarges the outlets below.

If in addition, the urogenital diaphragm, sphincteric muscle group, or the perineum be extensively lacerated, the uterus can prolapse to a still greater degree. Stretching or tearing of the rectovaginal prolongation of the endopelvic fascia completes the picture of prolapse with rectocele and possibly enterocele.

Advantages of Vaginal Hysterectomy in the Repair of Prolapsus

Adequate reconstruction of the pelvic floor demands recognition and repair of all damaged structures; at the same time removal of irreparable, diseased, offensive or potentially troublesome tissues is indicated.

It is not enough, one would readily admit, to do an anterior colporrhaphy and a perineorrhaphy in a case of prolapsus. It is not enough to do as well an amputation of the cervix—even a high amputation. It may not be enough, either, to supplement these by bringing the lower portion of Mackenrodt's ligaments together in front of the amputated cervix, or even overlapping them with one or two sutures, especially if the uterus is large and the ligaments are poor. If high rectocele or enterocele or both are present, they must also be dealt with, and too often the repair of the upper posterior vagina is neglected.

Vaginal hysterectomy proffers ease in the complete management of all conditions related to prolapse. The sagging uterus is removed, giving free access to all the supporting structures possible: the uterosacral ligaments; the entire depth of the lateral cervical ligaments, with their lower smooth muscle and upper strong fascial components; the frequently thick and strong upper broad and round ligaments which may now be used as definite aids in supporting the new pelvic floor as well as the bladder. And finally, in the presence of enterocele or high rectocele, no other operative procedure can give equal exposure for their rectification.

One occasionally hears the opinion that the uterus is better left in, to act as a central supporting hub to which the stretched ligaments may be fastened. Yet do we worry about the vaginal vault when total abdominal hysterectomy is done? And is it not true that besides restoration of the pubocervical fascia, the main support usually given when vaginal hysterectomy is not performed, consists of one or two sutures, drawing the lower parametrial tissue together

VAGINAL REPAIR COMBINED WITH VAGINAL HYSTERECTOMY*†

J. E. HARRISON, M.D., C.M., VANCOUVER, B. C.

IT IS not intended herein to divulge some novel or simplified surgical procedure for vaginal repair with vaginal hysterectomy in varying degrees of prolapsus. Rather it is hoped to focus attention upon a sound operation which presents distinct advantages over certain other treatments of this affliction, and yet which is not commonly applied. It is felt that from experience gained through even a relatively small series of cases one might point out a few helpful ideas in a technique which, to be consistently successful, must be meticulous. Most of the literature on this subject to date lacks detail in description and passes over some of the important as well as some of the most difficult steps in the operation as if they did not exist.

Time will not here permit detailed discussion of anatomic considerations. The recent publication "The Pelvic Floor in Parturition" by Richard Power of Montreal, in *Surgery, Gynecology and Obstetrics*, September, 1946, treats this portion of the subject so well that one could do no better than to recommend its careful perusal. Suffice it to mention here the supporting pelvic structures which one must be familiar with, in order to reconstruct properly a broken-down pelvic floor after vaginal hysterectomy.

First.—The endopelvic fascial diaphragm or upper pelvic fascial floor, composed of (a) an anterior segment or pubocervical layer, representing the platform which supports the bladder; (b) the strong lateral segments or condensations, known as Mackenrodt's ligaments, or the lateral ligaments of the cervix; (c) the posterior segments or condensations known as the uterosacral ligaments. All three of these segments having attachment to pelvic bony structure, and to a definite fibrous fascial capsule, forming a collar about the supravaginal cervix. The rectovaginal septum is an extension of this capsule which descends caudally from its posterior margin, between vagina and rectum to terminate in the perineal body.

Second.—The smooth muscle diaphragm in the base of the broad ligament, lying between the endopelvic fascial diaphragm and the upper surface of the levator ani muscle. Smooth muscle bundles radiate from the uterus at the level of the internal os, imbedded in fibrous tissue below the upper pelvic fascial floor, and enter into the composition of the ligaments just mentioned.

Third.—The levator ani muscular diaphragm, whose anterior segment, the pubococcygeus muscle, forms the largest, strongest, and thickest part of the pelvic floor.

Fourth.—The urogenital diaphragm, composed of two leaves of fascia and containing mainly the sphincter urethrae, and deep transverse perineal muscles.

Fifth.—The sphincteric muscle group, whose action is only very slightly supportive.

Sixth.—The perineal body, whose importance in this connection is because each one of the diaphragms constituting the pelvic floor has an insertion into it.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

†For lack of space, it is not possible to include all of the illustrations submitted, but only those showing the essential features of the operation.

should not be considered, this argument does not face the light of fact. On the contrary, one is almost invariably impressed in cases of prolapsus, not only by the sense of physical well-being, but by the sense of mental relief which follows removal of the so-called offending organ.

Occasionally after repair with vaginal hysterectomy the patient is left with too short a vagina. Many of these cases are in the older age group to whom this complication is usually unimportant. It happens chiefly in the patients with complete sacropubic hernia, and in these instances one is likely to finish any type of operative procedure with a shortened vagina. In the younger group where the vagina is not already contracted, it is rare if certain principles in technique are adhered to.

Indications for Vaginal Hysterectomy With Vaginal Repair

Under this heading come first the group of women who are at or near the menopause, who have badly ulcerated tissues, severe bleeding, or irregular spotting, all of which arouse anxiety or fear of cancer. Even for the gynecologist and/or the pathologist, it is not always easy to exclude cancer by biopsy, either grossly or microscopically. In this age group also severe dysmenorrhea may logically be considered an excuse for hysterectomy when vaginal repair is done. The patient is relieved at once of a painful or bleeding organ.

In this and older age groups, where cervical cystic disease or hypertrophy indicates amputation of the cervix, is it not sound judgment to remove the whole organ, and thereby exclude the possibility of subsequent fundus cancer? We all apply this same principle in our modern concept of proper procedure in abdominal hysterectomy, and although admittedly cancer of the cervix is more common than cancer of the fundus, the latter is nonetheless a real hazard.

In women past the menopause it would seem too, apart from the advantages in repair of prolapse, that for the same reason, a logical prophylactic measure would be to remove an organ which is beyond physiologic usefulness.

In the younger age group other indications to be considered are cases of fibromyoma of the uterus, adenomyosis, intractable severe bleeding, and perhaps some instances where sterilization is deemed necessary.

A very real indication for vaginal hysterectomy with vaginal repair are those cases on whom previous inadequate repair has been done, with abdominal fixation of the uterus, and where there has been subsequently, recurrence of vaginal prolapse with the cervix remaining high. In these cases the uterus must first be released by laparotomy, followed by its extirpation through the vagina with proper restoration of the pelvic floor.

Contraindications

Removal of the uterus in the course of repair is definitely contraindicated in the younger women who have not yet completed their families. The other contraindications are fixation of the uterus or adnexa by old inflammatory disease or endometriosis, and intraligamentous or retroperitoneal growths or previous operations which might complicate procedure.

in front of the cervix? With vaginal hysterectomy all ligaments are shortened as indicated by the degree of prolapse, their stumps are firmly united on each side and then to their fellows on the opposite side. They are anchored securely to the subpubic fascia beneath the urethra, and finally the anterior vaginal wall is made fast to them. The ultimate effect, without the previous downward pressure of the sagging uterus, is that the contraction and shortening of the ligaments actually lift up the anterior vaginal wall and the vault.

Vaginal hysterectomy with repair is to be recommended in preference to high amputation of the cervix in any case, first, because with poorer exposure and subsequent reconstruction of the cervix there is more likelihood of damage to ureters, and second, because if the patient is in the childbearing age there is danger from future pregnancy.

There are also distinct advantages in this procedure over the method of vaginal repair plus abdominal hysterectomy in cases where removal of the uterus is indicated. There is less risk of injury to ureters and bladder, less risk of peritonitis, postoperative ileus or shock. In the fat or aged or debilitated patient it may be done easily and without shock under local anesthesia.

The advantages of vaginal hysterectomy over Watkin's interposition operation are self-evident. The latter does nothing which the former cannot accomplish, and of course leaves in an abnormal and awkward position a uterus which may become troublesome.

The operation for vaginal repair plus abdominal ventrofixation of the uterus needs mention only for condemnation as unsatisfactory and as an unnecessary hazard for the patient. Too frequently the surgeon who does this type of operation depends upon the fixation of the uterus to correct the prolapse, and so does an incomplete repair of the vagina. Many of these cases appear later with a recurrent cystocele or enterocele, and yet the cervix is held so high by ventrofixation that proper vaginal repair, alone, is impossible.

The patient who has had two or three repairs, and still has prolapse, is an ideal candidate for vaginal hysterectomy. Here one has access to an unused set of supporting structures, in place of old ones attenuated by repeated dissection and scarring.

Disadvantages

Vaginal repair with vaginal hysterectomy is definitely a more difficult and painstaking procedure than others, but if one familiarizes oneself with the technique it is not more dangerous, and in many instances is less dangerous. It is more time consuming excepting the case where repair and abdominal hysterectomy are done, but if the time consumption be not fatal to the patient, this should not be considered in comparison to the many other advantages. We all do the more difficult and longer operation of total abdominal hysterectomy rather than subtotal, because we believe it is a better operation for the patient.

One hears that it is bad physically and psychologically for a woman to lose her uterus, and with it her menses. Excepting the young woman who has not yet completed her family, and therefore of course, where the operation

The left index finger is carried through the cul-de-sac opening behind the right uterosacral ligament, to a point above it and close in to the uterus. Having decided how much tissue is to be ligated, depending upon the thickness and depth of the uterosacral and lateral cervical ligaments, a crushing clamplike heavy Oseiner forceps is applied for a moment to thin out and groove the tissue. This is removed and replaced by a ligature of No. 2 chromic catgut, carried through by a ligature carrier from the anterior surface of the parametrium, to the tip of the index finger close to the uterus in the cul-de-sac. A small but useful point in the tying of fairly large "bites" of parametrial tissue is that the assistant should relax his pull on the cervix as the knot is made. Otherwise tension on the tissues will prevent a securely fastened knot. The crushing of the tissue first also makes possible a more securely tied ligature, and the grooving insures against subsequent "slippage." The ligature is held long and the parametrium and uterosacral attachment is divided at least one-fourth of an inch distal to it. Provision of a generous stump distal to the ligature also prevents ligature "slippage."

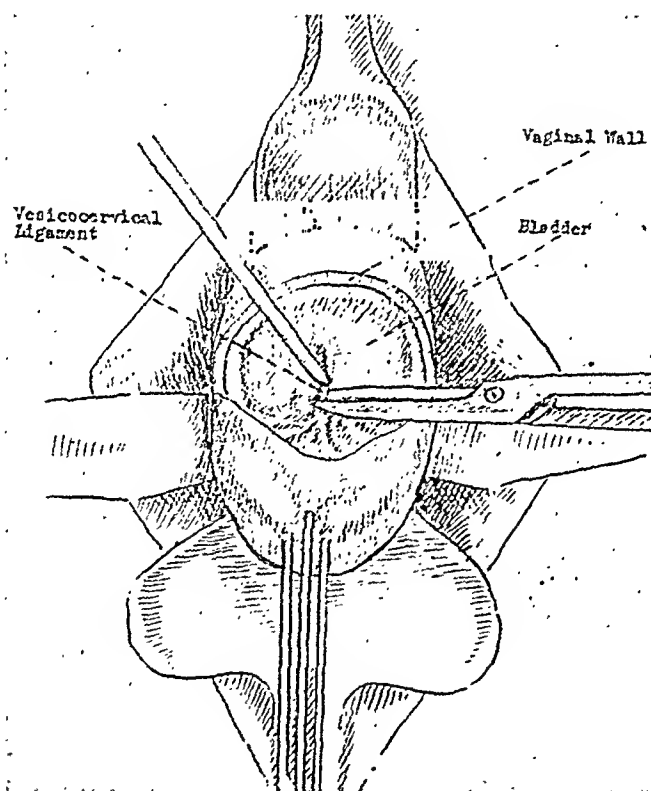


Fig. 1.—The vesicocervical ligament, extending to the cervix from the junction of the floor and posterior wall of the bladder, has been caught with toothed thumb forceps and lifted up to appear as a sagittal fold. This fold is placed on tension by traction on the floor of the bladder toward the symphysis, and is incised with scissors held at right angles to it, midway between bladder and cervix, to open the vesicocervical space.

Carrying the finger higher up the posterior surface of the parametrium, this crushing, ligation, and division of supporting structure is repeated once or twice, depending upon the depth of tissue forming the ligament of Mackenrodt. These ligatures are held long in one forceps. The uterine blood vessels are easily recognized and ligated close to the uterus. This ligature is cut short, so that it cannot be pulled off subsequently. The parametrial supports and vessels on the left side are now ligated and severed from the uterus in the same manner. With each step, the uterus pulls down more readily, exposure improves, and with the main blood supply interrupted, bleeding is negligible.

Technique

If the operation is performed under anesthesia other than local, blood loss may be greatly diminished by preliminary injection of one-half cubic centimeter of pituitrin into the lower parametrium on either side.

The anterior lip of the cervix is pulled well down with volsellum forceps, and the anterior vaginal wall incised transversely just above the point at which it becomes fixed to the cervix. If incision is made below this point, one may have difficulty in identifying the vesicocervical ligament, through which entrance is easily gained to the space between bladder and cervix. The incision is carried through mucosa and fascia, so that it will gape widely with upward retraction of the vaginal wall, and expose clearly the juncture of bladder and cervix. To further improve exposure one may dissect the anterior vaginal wall from the underlying bladder with curved blunt-pointed scissors, upwards for an inch or so, dividing the freed wall in the midline and retracting the mucosal edges. This will give full view of the vertical fibers of the vesicocervical ligament, which separates the vesicocervical from the already opened vesicovaginal space. The ligament is grasped with toothed thumb forceps, lifted up to appear as a sagittal fold (Fig. 1), and is incised with scissors held tangent to the surface of the bladder midway between bladder and cervix. This opens the vesicocervical space from below much more accurately than can be done with blunt gauze dissection. With traction downward on the cervix, first one index finger and then both are slipped up into the loose connective tissue beneath the bladder (Fig. 2) to separate the attachments between bladder and uterus completely. One not only reaches upward as high as possible, but separating the fingers widely, pushes laterally to free the base of the bladder and the ureters from the broad ligaments beneath.

The cervix is next pulled toward the symphysis, a posterior weighted speculum holding the vaginal tissues toward the sacrum. A transverse incision is made through mucosa and fascia of the posterior vaginal wall at the same level as that already made in the anterior wall. This incision may not overlie the tip of the pouch of Douglas, especially if the cervix be hypertrophied and elongated, but an incision made further down the posterior wall than this would shorten the vagina accordingly, and should be avoided. One may divide the wall vertically in the midline from this point downwards until the peritoneum is reached, and remembering the proximity of the rectum to vaginal wall, the opening into the peritoneal cavity should be made close to the uterus. The peritoneum of Douglas' pouch is incised transversely, and its lower margin made fast with a suture to the adjacent margin of the vaginal wall. A wide posterior speculum is then slipped into the pouch of Douglas, and, if omentum or bowel is seen, the head of the table is dropped to carry them up out of the operative field, or a taped sponge is placed within the cul-de-sac. If unusual difficulty is encountered in finding the peritoneum of the cul-de-sac, due perhaps to obliterative adhesions within, the uterovesical pouch of peritoneum is opened and a finger is carried down behind the uterus to push the cul-de-sac forward through the posterior wall incision into plain view.

The ends of the anterior and posterior vaginal incisions are joined by lateral incisions through mucosa only, and the upper leaf of the mucosa on either side is pushed with gauze well up to the level of the internal os. Superficial fibres of the lower parametrium are snipped and also pushed up, to carry a possible vagrant low-looping ureter out of harm's way.

A wide retractor is now placed beneath the bladder in the uterovesical space (uterovesical peritoneum still unopened), and, holding the bladder well forward, the cervix is pulled posteriorly and to the patient's left, thus drawing the right ureter well away from the uterus.

The entire border of the peritoneal opening into the pelvis is now exposed, and just external to it, lying on either side, are the stumps of the uterosacral, lateral cervical, and upper broad ligaments. These upper and lower ligament stumps with intervening endopelvic fascia are next sutured together on either side, so as to make two lateral massive ligamentous supports which will be united later to form the new pelvic floor.

Closure of the peritoneal cavity is effected with a purse-string suture of No. 1 plain catgut, placed just above the free edge of peritoneum inside the broad ligament stumps (Fig. 4). Care is exercised to avoid large blood vessels and ureters by taking shallow bites with the needle. In the presence of an enterocele, the purse-string suture crosses the cul-de-sac at a sufficiently high level to exclude all redundant peritoneum. This is then dissected out and excised. To facilitate the placing of the purse string, which can be difficult, it is safer to draw down the broad ligament stumps with forceps, rather than to pull them down by their ligatures. Inclusion of ovary, omentum, bowel, or the finmbriated tube end, must be avoided as the purse string is tightened.

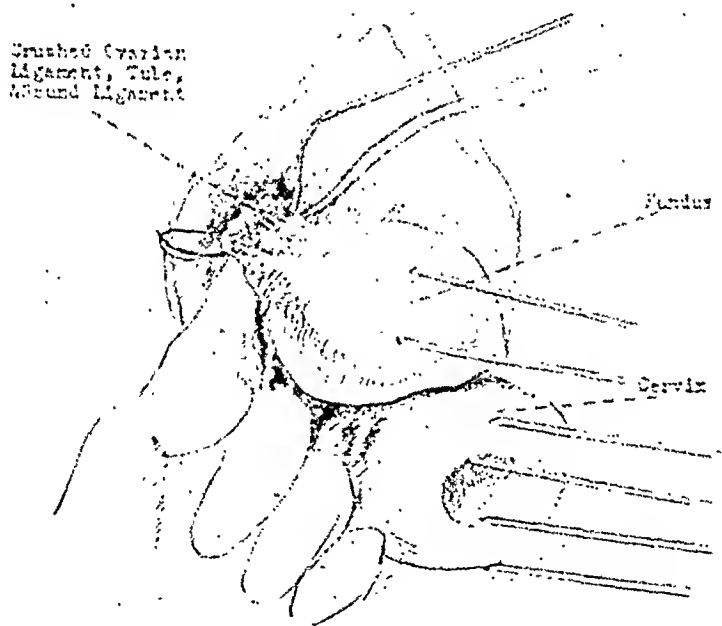


Fig. 3.—The fundus of the uterus has been drawn through the opening in the vesicouterine pouch of peritoneum. The right ovarian ligament, tube, and round ligament have been crushed, and a chromic catgut ligature is being placed to tie off these structures before cutting them away from the uterus. A stump a quarter of an inch long is left distal to the ligature. The remaining broad ligament below these structures is ligated and cut away from the uterus.

Repair of cystocele or urethrocele is now begun by dissection with curved blunt-pointed scissors to free the vaginal mucosa from the underlying fascia. The vaginal wall is divided in the midline to just below the urethra, and flaps raised laterally to expose the redundant bladder. On each side of the urethra, the dissection should be carried to the pubic arch to break down old traumatic adhesions which may interfere with sphincteric function. The strong sub-urethral fascia (cranial portion of the urogenital diaphragm) covering the neck of the bladder is plicated with two or three superimposed mattress type sutures of No. 0 chromic catgut. The importance of this minor procedure in every case cannot be overemphasized, for not uncommonly has the preparation of the anterior wall for repair, without this precaution, caused incontinence in

The uterovesical fold of peritoneum is easily identified and is incised transversely. Its upper edge is secured with one or two sutures held long to prevent its retraction upwards behind the bladder, and the retractor under the bladder is replaced by another inserted into the uterovesical pouch. The fundus uteri is grasped with a single toothed volsellum forceps and "tugged" out through this opening. In some instances this maneuver is facilitated by replacing the cervix in the upper posterior vagina. Depending upon the size of the uterus, it may be necessary to deliver the fundus with successively applied tenacula. In the case of the larger fibroid uterus this is supplemented by cutting out wide deep wedges of tissue held in the tenacula until the fundus

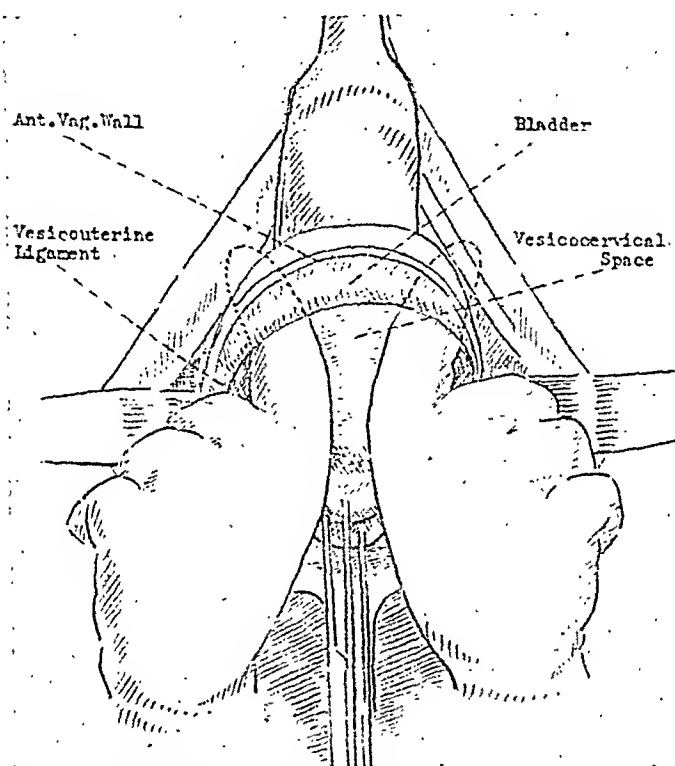


Fig. 2.—The vesicocervical space is entered with the index fingers, and as traction downward is made on the cervix, the bladder is freed from the uterus and broad ligaments, as high and as far laterally as possible. This is done to minimize the possibility of subsequent damage to ureters.

is small enough to deliver. At times one will encounter unforeseen adhesions involving bowel, omentum, or adnexa, but as the uterus is brought more fully into and through the opening, these may usually be dealt with simply. Particular difficulty may be overcome by bisection of the uterus, when the hand can be introduced into the pelvic cavity for further examination and exposure.

When the fundus is delivered (Fig. 3), the upper broad ligaments, including tube, ovarian and round ligaments, are first crushed with forceps as mentioned above, ligated with chromic catgut No. 2, and severed from the uterus, leaving a stump one-fourth of an inch distal to the ligature. The point chosen for ligation will depend upon the degree of prolapse, and the amount of shortening of the structures desired for rebuilding a firm pelvic floor. These ligatures are held long. The remaining portions of broad ligament are ligated and cut away to remove the uterus completely.

The anterior retractor is withdrawn from the uterovesical region of the peritoneal cavity, and replaced between peritoneum and bladder. The posterior retractor is withdrawn from the cul-de-sac and replaced by a short-bladed weighted speculum.

be extended downward toward the perineum. Usually, however, one incises the perineum transversely, and with blunt scissors dissects free the mucosa from the underlying rectovaginal fascia. In the higher, thinner central portion where the rectum is in closer apposition to the vagina, the mucosa is peeled off by gauze dissection. This should be carried up to the open vault of the vagina and the mucosal flaps raised laterally to expose the stronger lateral fascial regions, and in the lower vagina, the fascial covering of the levator ani muscles.

A crown suture (Fig. 6) is inserted at the vault, uniting the stronger lateral rectovaginal fascial areas and bases of the vaginal mucosal flaps to the uterosacral and lower broad ligament stumps above. The posterior wall fascia is then sutured with interrupted No. 0 chromic catgut (Fig. 7) uniting the fascia near the bases of the vaginal mucosal flaps and in the lower vagina, the sheaths of the levators ani.

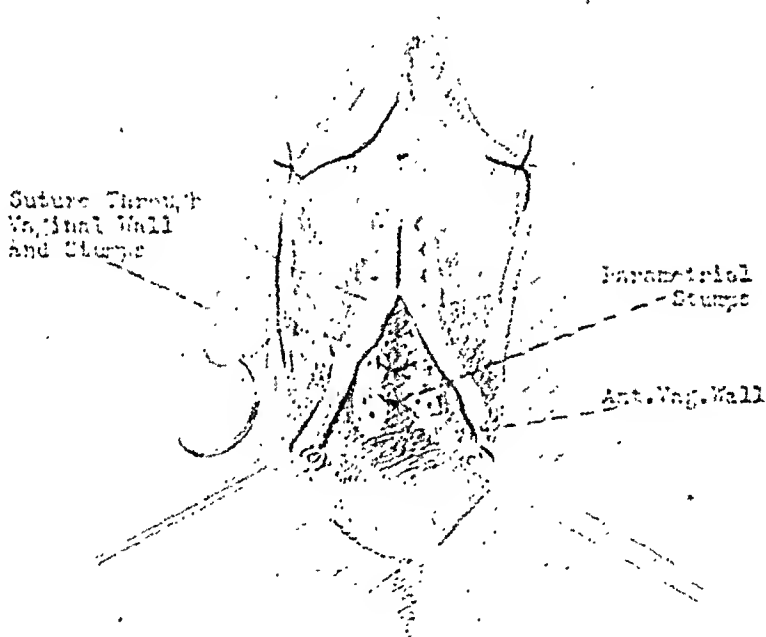


Fig. 5.—All upper and lower broad ligament stump ligatures on the left side have been tied to those on the right and cut short. Vaginal mucosa flaps have been trimmed and the margins are united with interrupted chromic catgut, several of these being passed deeply through the underlying broad ligament stumps. This not only firmly unites the ligamentous supports, but as they retract they will draw the anterior vaginal wall and vaginal vault upward, and increase the length of the vagina. The opening at the vaginal vault is closed excepting for insertion of a small gauze drain, unless high rectocele or enterocele must be dealt with. Then it is left open.

The mucosal flaps are trimmed and their margins united by a continuous stitch of No. 0 chromic catgut picking up small "bites" of the underlying fascia to close "dead space."

The lateral regions of the perineal incision are incised to permit withdrawal of the lower ends of the levator muscles, and these are united with interrupted catgut, the lower stitch picking up anterior fibers of the anal sphincter. The constrictor cunni muscle is restored by a single suture biting deeply into the labia majora. Transverse perineal muscles are united by a running suture of No. 0 chromic catgut which is continued subcuticularly to close the perineum.

a previously continent patient. In large cystoceles, the bulging bladder is reduced with a running suture uniting the strong lateral portions of pubo-cervical fascia.

The upper broad ligament stumps previously made fast to the parametrial and uterosacral stumps are now drawn out and forward with forceps to a position beneath the neck of the bladder. A mattress suture of No. 2 chromic catgut is passed through the subpubic ligament and fascia on the left, deeply through both upper broad ligament stumps to the right subpubic ligament and then back through the stumps to be tied at its point of entry. A second suture in support of this sling is passed from outside the base of the anterior vaginal wall flap on the left, through the subpubic ligament and stumps, and out through the right subpubic ligament and vaginal flap base to be tied later during closure of the anterior wall.

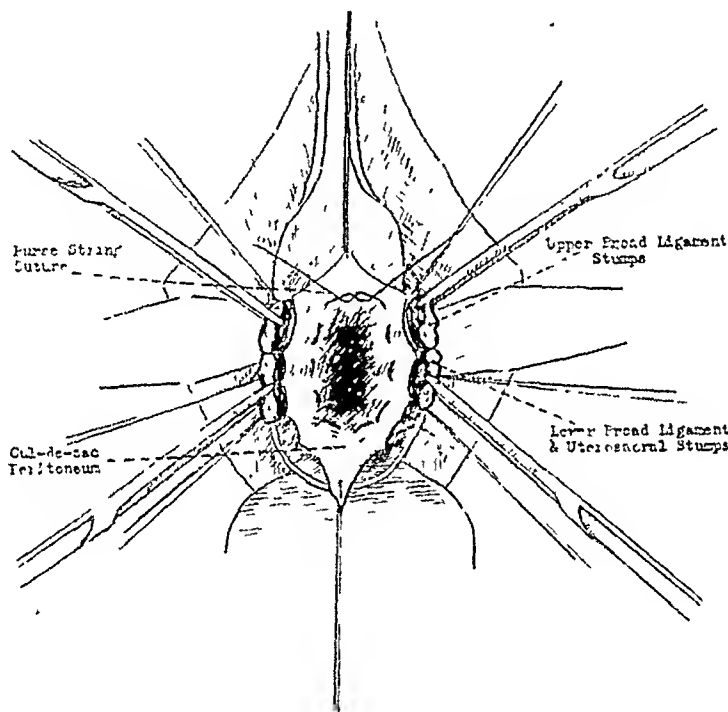


Fig. 4.—Upper and lower broad ligament stumps on each side are shown being drawn outwards and laterally by four forceps, to expose the entire peritoneal opening for insertion of the purse-string suture which will close it. The use of forceps makes it unnecessary to pull the stumps outward by their ligatures which might slip off. If enterocele be present, the purse string passes across the pouch of Douglas at a high level and excess peritoneum below is dissected free and excised.

Upper and lower broad ligament stump ligatures which have been held long are now tied to their fellows on the opposite side to unite the lateral halves of the new pelvic floor.

Excess vaginal flaps are trimmed, and the margins united with interrupted chromic catgut (Fig. 5). Three or four of these sutures are passed deeply through the underlying ligaments which later will contract and pull the vaginal wall up with them. A small gauze drain is left through the suture line near the vault to drain the stump area. It is removed on the fourth post-operative day.

If no enterocele or high rectocele exists, the vault may be closed and the operation completed by a low colporrhaphy and perineorrhaphy. In the presence of enterocele or high rectocele the vault is not yet closed. Incision through the mucosa may be begun where the cul-de-sac was previously entered and may

TABLE I. CASES, END RESULTS, AND COMPLICATIONS

| CASES | NUMBER | REMARKS |
|-----------------------|--------|--|
| Total | 77 | Average age—50.5 Oldest—85 Youngest—35 |
| Prolapse | | |
| 3rd Degree | 23 | Average age—50.3 |
| 2nd Degree | 15 | Average age—51.4 |
| 1st Degree | 39 | Average age—44.4 including such other indications as abnormal bleeding, severe dysmenorrhea, diseased cervix, large cystocele, etc. |
| Previous operations | 3 | Previous vaginal repairs with abdominal fixation of the uterus, and cervix high in vagina, necessitating laparotomy first |
| Fibroid uterus | 13 | Five cases of 3 to 3½ months' pregnancy size. Eight cases of lesser size. |
| Malignancy | 3 | Ages (a) 46, (b) 61, (c) 69 years. Cases (a) and (b) were adenocarcinoma of fundus. Both had postoperative x-radiation therapy. Both well and no recurrence at four and five years postoperative. Case (c) was an early squamous cell cancer of a protruding uterine polyp. No irradiation. Developed recurrence in vaginal vault in 1½ years and died four years after operation |
| <i>End Results</i> | | |
| Mortality | 0 | |
| Recurrence | | |
| Cystocele | 0 | Size of walnut above a low colporrhaphy. Patient apparently unaware because no complaints |
| Rectocele | 1 | |
| Enterocoele | 0 | At time of reading of paper one case was having nocturnal incontinence only. Since then she has cleared up entirely on estrin therapy |
| Incontinence | 0 | |
| <i>Complications</i> | | |
| Hemorrhage | 1 | Occurred on the 18th postoperative day from slight slough of upper posterior vaginal wall |
| Cystitis | | A common postoperative complication due to surgical trauma and frequent catheterization. Not more common than with other methods of repair. May be lessened greatly by strapping in a plain catheter, which is released when bladder fills (q 6 to 12 hours) and prophylactic administration of sulfadiazine, grs viiss q.i.d. for 5 days |
| Uterovaginal fistula | 0 | |
| Vesicovaginal fistula | 0 | |
| Rectovaginal fistula | 0 | |
| Small vagina | 8 | Average age 68 years |

Summary

1. The most important anatomical considerations are briefly outlined.
2. Advantages of vaginal hysterectomy in the repair of procidentia are discussed.
3. The disadvantages of the operation are considered.
4. A detailed technique of operation is described.

Conclusions

1. The literature on vaginal hysterectomy with vaginal repair to date, mainly lacks detailed description of operative technique.

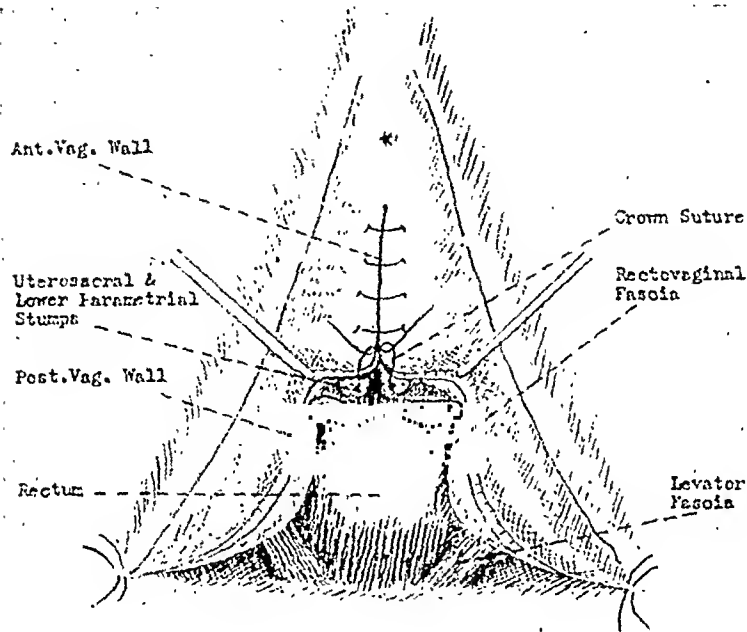


Fig. 6.—This figure shows exposure of the rectovaginal fascia up to the vault of the vagina, and the fascia covering the levator muscles in the lower vagina. In the vault are seen the posterior portions of the uterosacral and lower parametrial stumps. A crown suture of chromic No. 2 catgut has been placed to unite these stumps to the bases of the vaginal mucosa flaps, and the lateral portions of the rectovaginal fascia. This is an important step in the prevention of enterocele recurrence.

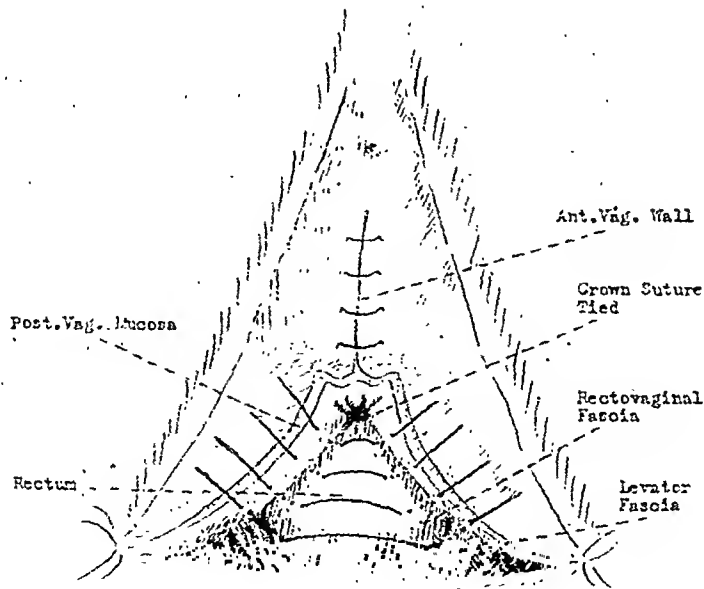


Fig. 7.—The vault of the vagina has been closed by tying the crown suture. A small gauze drain should be shown emerging from the anterior wall just above this point. The rectocele is reduced with interrupted No. 0 chromic catgut sutures, drawing together the bases of the vaginal mucosa flaps and the stronger lateral portions of the rectovaginal fascia. In the lower vagina these sutures include the anterior borders of the levator muscles and their fascial coverings.

STERILITY IN THE FEMALE*

KENNETH M. GRANT, B.Sc., M.D., C.M., HALIFAX, NOVA SCOTIA

THE problem of sterility has always assumed considerable importance in the practice of the gynecologist. In fact, there are few problems which test his training, patience, and breadth of knowledge more than that of sterility.¹ No less than 10 to 12 per cent of all marriages are barren. A number of gynecologic lesions may be factors in sterility, yet in recent years much light has been thrown on that large group of cases in which endocrine and physiological factors play an all-important role in its etiology.

The terms sterility and infertility are sometimes incorrectly designated as synonymous. According to Meaker² "sterility is the inability to initiate the reproductive process on the part of a couple who have desired and who have attempted to reproduce for a reasonable length of time, ordinarily at least a year." Some suggest three to five years, though less than 10 per cent of initial pregnancies occur after two years. "Infertility" is a term embracing any degree of conceptive capacity below the level of physiologic perfection, or the failure to produce a viable child.

From a clinical viewpoint, sterility in a mating is inability to reproduce, and the fault may be that of either the male or female or both, hence the fertility of a couple must be considered.³

Absolute sterility is a condition in which conception is clearly impossible. It is generally due to congenital malformation, such as absence or atrophy of the uterus or gonads, absence of vagina, or to complete occlusion of the Fallopian tubes or ductus deferentes, or when destructive disease has rendered one incapable of fertilization.

Relative sterility is one in which conception may occur, but various factors may make it difficult until existing precluding factors in either mate are corrected. Examples of such include endocrine and metabolic dyscrasias as well as local anatomic defects or lesions.

Acquired sterility is usually considered as the failure of conception after one or more children. It may be due to injuries, operations, new growths, metabolic disturbances, etc.

Selective sterility and fertility are terms used where an individual proves fruitful by one mate but barren by another.

Since the scope of this paper is primarily intended to cover the couple who present themselves seeking a reason for lack of conception, no attempt will be made to cover the subject in minute detail, but rather to outline a reasonably thorough and effective plan of investigation and treatment where indicated.

From the title of this paper one might infer that the female is altogether at fault. Such is certainly not intended, however, as the male partner must bear a considerable portion of fault in the study of childless marriages. Al-

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

2. It is felt that this lack of detail may contribute to the fact that the operation is not performed more widely by gynecologists.
3. Removal of the uterus during the course of vaginal repair is indicated far more frequently than it is practiced.
4. The operation presents distinct advantages in selected cases over any other form of treatment of procidentia.
5. Gynecologists in general should be encouraged to perform this operation.

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Discussion

DR. B. P. WATSON, New York, N. Y.—I should like to congratulate Dr. Harrison on one of the best expositions of the anatomy of the essential supports of the pelvic organs and the techniques for their repair that I have ever heard.

I agree with him entirely in his indications for vaginal hysterectomy. After child-bearing is over the uterus has no physiological function, and it should be removed if in doing so a better and stronger support to the pelvic diaphragm can be given.

It is essential in any repair to make sure that the vault of the vagina is properly supported, otherwise it may prolapse later, no matter how good a lower pelvic floor repair has been done.

The only detail which I seem to pay a little more attention to than does the speaker is in isolating the supporting fascia of the lower rectum and uniting it in front of any rectocele which may be present.

DR. HARRISON (Closing).—Dr. Campbell mentioned the larger uterus. I would agree that in the presence of various types of pelvic pathology, it would be difficult to peritonealize raw areas. This does not necessarily apply to the fibroid uterus. Quite a few fibroid uteri up to three to three and one-half months' pregnancy size have been removed per vaginam without undue difficulty. This has not been done without some degree of relaxation of the vagina, or prolapse. I would agree, if any operation involved difficulty in closing the peritoneum cleanly. In two or three patients who had had previous Gilliam suspension operations, and whose round ligaments had stretched with prolapse, utilization of these ligaments and peritonealization was not a problem.

I did not say, Dr. Campbell, that I use a running suture in the anterior wall, because I never do. I did say that if the cystocele were of such a size that it required reduction and additional support, a running suture is used to plicate the fascia covering the bladder above the repaired sphincter. The vaginal mucosa is closed with interrupted sutures and some of these should extend deeply to include the underlying ligament stumps.

I have experienced no trouble with estrogen regarding increased friability of tissue. I do not see what would be gained by two or three days' treatment. This, in my opinion, could not improve the circulation and the tone of the tissues sufficiently. I have given small quantities orally over a period of three to four weeks before operation and have not run into the difficulty mentioned.

One should note particularly the history of acute general infections (scarlet fever), debilitating diseases, nephritis, venereal diseases, appendectomy (especially if patient had drainage), and pelvic operations. (2) A complete physical examination; routine blood and urine tests; evaluation of endocrinological stigmata. (3) A careful examination of the female generative tract, with special reference to the cervix. (4) Examination of the semen. (5) Hühner postcoital test. (6) Tubal patency tests. Hysteroграмms. (7) Investigation of the endocrine system.

Most, if not all, of the above investigation can be carried out in three office visits or less, depending on the findings. (To obtain the history of a couple, it is usually advisable to consult each one at separate times. In this way premarital incidents are more freely discussed and may be of value in the investigation.)

At her first visit the medical history should incorporate special reference to sexual activity and habits (coital, dietary, etc.), a careful menstrual history, for the menses can usually be considered a fair index of the reproductive development of the patient. Irregularities should be carefully noted and considered as possibly connected with ovarian dysfunction, whereas normal cyclic bleeding, while usually indicating normal function, may occur with anovulatory cycles. Her husband's health should be inquired into, as well as any other factors concerned with sterility, such as difficulties with the sexual act, or the actions of the female partner following intercourse. She is then given a complete physical examination, which should include routine blood tests and serology, urinalysis, and blood pressure. A clinical evaluation should be made of any endocrinologic stigmata from her skeletal configuration, her height, weight, distribution of hair and fat and secondary sex characteristics. Although all of the endocrine glands are more or less intimately related, in fertility it is becoming more apparent that the pituitary is essentially the gland of greatest importance, because of its direct action on the gonads, and indirectly on the thyroid, adrenals, and others.

After the medical examination, the gynecologic examination should follow, and include not only the pelvic but the functional examination as well.

Pelvic examination.—

Special points to be noted are:

1. *Infection in the lower genital tract, including the cervix:* The eradication of vaginal and cervical infections often yields the most gratifying results, and must at least be considered contributory factors in some cases. It may not be easy to explain why such infections as *Trichomonas vaginitis* and erosion of the cervix produce infertility in some and not in others, but their removal has certainly resulted in pregnancy in not a few of my own cases. This is especially true of erosion of the cervix, the cauterization of which ranks high as a therapeutic measure in sterility. (Caution should be exercised in too deep cauterization and cauterization very soon after the cessation of the menstrual flow to avoid secondary hemorrhage which may be very troublesome.)

though some estimate the male to share or accept full responsibility in more than one-half of the cases of childless union,⁴ in my own series the incidence was slightly less than 25 per cent. Percentages undoubtedly vary under different social and racial conditions.

In the investigation of sterility in the female, a balanced outlook must be maintained. Laboratory methods, though necessary, should not be depended upon entirely, but incorporated with the results of investigations of the reproductive system in particular and the clinical examination of the patient as a whole.

Parker⁵ states, "In order to evaluate the individual case properly the complete cooperation and examination of both partners are essential. The complexity of the problem, at times, and the necessity for repeated examinations must be impressed upon them."

Complete investigation into such a case and its proper treatment may be so complex and distributed over such a wide field as to involve the internist, the gynecologist, the urologist, the endocrinologist, the psychologist, as well as the roentgenologist. Such an inquiry has obvious and practical advantages, such as the elimination, for one thing, of much worthless and harmful treatment of a sort all too prevalent and, in particular, such disasters as operations done for sterility upon the wives of absolutely sterile men. Only if one partner is found to be incurably sterile is it permissible to dispense with the investigation of the other. Also by means of a complete study the most efficient treatment will be effected.⁶

It is obvious, of course, that pregnancy can occur only when the following conditions obtain⁷: (1) Healthy sperm must be deposited at or within the cervical canal. (2) The sperm must be able to ascend without interference and at the proper time to fertilize a healthy ovum. (3) The ovum must implant itself on a suitably prepared endometrium.

Incidence.—Douglas⁸ states that 70 per cent of sterile couples show more than one causative factor. In a series of 48 unselected private patients, a single factor was noted in almost 60 per cent of them, and several factors were not commonly encountered.

Investigation.—Gardner⁹ states that many factors may contribute to the causation of infertility and that it is necessary to discover and correct as many of these as possible in order to achieve success. The examination should be thorough, can be done efficiently, and much discouragement avoided by adopting a simple but definite plan of investigation and completing it.

The day is fortunately passing, I believe, though repercussions of it are still noted, when a woman complaining of sterility is first advised to have a dilatation and curettage or to have a retroverted uterus corrected by operation, or because of an infantile uterus she is not likely to become pregnant, before a proper inquiry and investigation are carried out, preferably on both partners. Stein¹⁰ says, "the dilatation and curettage are often dispensable, the retroversion often of little consequence, and infantile uterus is usually an inaccurate diagnosis."

The diagnostic inquiry should include the following: (1) A complete medical history preferably of both partners, with special reference to sex history, coital habits, dietary habits, etc., should precede special sterility studies.

If a pelvic examination under anesthesia is indicated, as when findings are difficult to evaluate, the time of choice would be just before the onset of the menstrual flow, when an endometrial biopsy can be performed.

There is apparently some disagreement among gynecologists whether uterine fibroids play much part in causing sterility. I feel they are not particularly important unless of such profound size as to distort the cavity of the uterus or cause blockage to the Fallopian tubes. They are more likely to alter the course of a pregnancy rather than preventing its initiation.

Bilateral cystic ovaries, either as a result of hormonal imbalance or new growths certainly play a role in sterility, as pregnancy is a rarity in such cases.

4. *Examination of the semen:* Heekel¹¹ states that "the final diagnosis of the relative sterility or fertility of a man can be made only by the appraisal of the seminal fluid." If the semen conforms to the normal standards, further examination of the husband is probably not necessary; if not, a physical examination of the husband should be done with special reference to undescended testes, testicular atrophy, and metabolic or endocrine disturbances.

After several days of continence the specimen is preferably collected in a clean and dry glass container, following coitus interruptus, transferred immediately to a clean test tube, corked and placed in sufficiently close proximity to the body to maintain reasonable warmth, and brought to the office or laboratory within an hour. The collection by means of a condom, under similar conditions, in my own experience, does not seem as hazardous to the motility of the sperms as most authorities would have us believe, and I use this method frequently, as less handling is entailed and more constant temperature assured.

The important feature of the examination is the sperm count. Using a white blood counting pipette, diluting 1:20 with 5 per cent sodium bicarbonate solution, counting five blocks of sixteen squares and adding six zeros. An average normal specimen should contain approximately 100,000,000 spermatozoa per c.c., at least 80 to 85 per cent normally formed, and 75 to 90 per cent should exhibit active motility for some hours at room temperature.

The stained smear is also important, and less than 20 per cent should be abnormal.

It would seem wise, therefore, to refer to an interested urologist all husbands whose semen does not conform to those criteria just mentioned.

5. *Hühner postcoital test:* Though the next step usually undertaken is that of determining the patency, or nonpatency, of the Fallopian tubes, the Hühner test is now described as being more in keeping with the preceding paragraph. This is a simple and informative procedure, and requires only a few minutes. It should be performed at the time of ovulation, which is fourteen to fifteen days before the expected onset of the next menstrual period, when the cervical mucus is most receptive to sperms. It is wise to instruct the patient to empty her bladder and rectum before intercourse, and to report for examination within two to three hours following it, without taking a douche.

Samples are aspirated from the vaginal pool and from one, or preferably two levels in the cervical canal and placed on a slide, a cover glass placed over each and immediately examined under the microscope. Within the time allotted

The mere probing of the cervical canal by passing a uterine sound (a procedure I now do routinely at the first visit) has given such remarkable results, that in cases where no other gross abnormality exists in the pelvis I advise the patient to curtail further investigation a few months and await results. I feel some of the credit given to the insufflation of patent tubes rightly belongs to the passage of the cannula through the cervical canal.

It need hardly be emphasized that routine smears of the cervix and urethra to exclude gonococcal infection, and examination of Skene's and Bartholin glands should be made.

2. *Structural abnormalities:* In this group would fall those cases of arrested development of vulva, vagina, uterus, adnexa, the absence of one or more, and cases of unruptured or rigid hymen. Hypoplasia of the uterus can usually be suspected when the uterus is about the size of a small walnut, usually anteflexed but may be difficult to outline by palpation (if patient is fat) and when a long, conical cervix with pinhole external os is found. Though hypoplasia of the uterus does not invariably signify sterility, it is a rather common finding in many cases.

3. *Malpositions of the uterus and adnexa:* Retrodisplacement of the uterus has certainly been overemphasized, in the past, as a cause of sterility. However, when associated with a cervix which points toward the anterior vaginal wall, or behind the symphysis and away from the seminal pool, it assumes more importance as a factor. It is well known that many women with such findings readily conceive, and it is no longer common practice to radically correct such displacements. When such a uterus is mobile, it is much less likely to be a cause of infertility than one which is fixed by adhesions resulting from inflammatory disease or endometriosis. The use of a Hodge pessary in such cases, either with or without manual replacement of the uterus, is often successful as a therapeutic measure.

4. *Pelvic inflammatory disease:* Since this is one of the commonest causes of sterility, the adnexa must be completely palpated. It is manifested by the usual signs of tender tuboovarian masses, or indefinite thickening of the bases of the broad ligaments, partial or complete fixation of the uterus, and tenderness on movement of the cervix.

Endometriosis is probably often overlooked as a cause of sterility. I believe it is a rather frequent cause. I can recall several cases in which, on investigation, no known cause could be found for the sterility of the couple, but examination and operation sometime later revealed the presence of a well-established endometriosis. The explanation in early cases is difficult, as the Fallopian tubes are patent, ovulation is rhythmic, yet pregnancy is a rarity. The condition should be suspected when the patient complains of increasing dysmenorrhea which has been acquired during adult life, when the uterus is retroflexed and fixed, when the ovaries are enlarged, tender, and fixed, and when pain is referred to the rectum at the time of ovulation as well as at menstruation.

In my own practice, in most, though not all cases, choosing the proper time of the cycle, the patient is sent into the hospital for about twenty hours. On the morning following admission a basal metabolic rate is taken. Following this a hypodermic containing $\frac{1}{6}$ grain morphine and $\frac{1}{150}$ to $\frac{1}{200}$ grain scopolamine is given as a sedative and antispasmodic, and an hour later the tubal insufflation and lipiodol injection are carried out. (Methyltestosterone, given orally, in doses of 50 to 100 mg., serves as an excellent antispasmodic, especially when insufflations are carried out in office practice.) It is rarely necessary to use more than 6 or 7 c.c. of oil injected slowly. It is preferable, though not necessary, to watch the instillation through a screen, following which an x-ray is taken. A nonopaque speculum is desirable. Within six to seven hours another plate is taken to determine whether the lipiodol has passed into the peritoneal cavity. If not, the patient is instructed to return in forty-eight hours and another plate taken.

In most cases, where tubes are patent, little or no residue of oil is noted; where the tubes are blocked, it is still plainly visible within them.

The contraindications to the use of tubal insufflation and hystero-graphy are well known and include recent acute or subacute pelvic inflammatory disease, purulent cervical discharge with endocervicitis, infected urethral or Bartholin glands, menstruation or abnormal bleeding, following dilatation and curettage, cardiovascular and pulmonary disease, suspected pregnancy, and severe nervous disorders.

7. *Investigation of the endocrine system:* Gardner says,¹² "Healthy women of childbearing age, who menstruate normally and with some degree of regularity, probably also ovulate fairly regularly. However, individuals without gross genital pathologic changes, who either menstruate infrequently, flow irregularly and scantily, or bleed continuously, probably do not ovulate, such menstrual disorders usually resulting from disturbed function by the glands of internal secretion."

If the investigation so far reveals no obvious cause of sterility, the question of determining whether ovulation is occurring becomes important. Ovulation is difficult to prove. Only presumptive evidence of it may be obtained by endometrial biopsy, taken a few days before the onset of menstruation, or preferably shortly after its onset, to avoid the risk of interrupting an early pregnancy. Ovulation is assumed when the endometrium shows the secretory phase of corpus luteum stimulation. The procedure, however, occasionally is difficult to do, causes not a little pain in nulliparous women especially, and really gives information only for the one cycle reviewed. Recently I have used endometrial biopsy less, and basal body temperature curves more, and have been impressed by its advantages and usefulness. A pronounced biphasic curve is regarded as evidence that ovulation has occurred. At least two cycles must be taken.

Vaginal smears, and determination of the pregnandiol complex between the twentieth and twenty-fourth day are less reliable measures.

The number of cases of hypothyroidism seen in my own practice far exceeds that of any other endocrine problem. Even mild degrees of it are often asso-

above, if numerous actively motile sperms are seen in both samples, or five to fifteen active sperms present in the mucus from the cervical canal, one can then assume that intercourse has been properly consummated, that sperms are capable of ascending the cervical canal, and that endocervical secretions are receptive to them. Under such conditions one need not feel concerned about the position of the cervix, the length of the vagina, minor abnormalities of the male, such as epispadias, hypospadias, or premature ejaculation. If dead spermatozoa are found in the samples taken from the cervical canal, and active ones found in the vaginal pool, one can properly assume that some hostility exists between the sperms and the endocervical secretions. In such cases, eradication of the endocervicitis undoubtedly present will often result in curing many cases of sterility. I have found such a procedure pays dividends in very many instances. A word of caution is hereby interjected, however, against too extensive cauterization, such as conization, etc., owing to the extensive scar tissue formation which invariably follows such procedures.

6. *Tubal patency and hysterosalpingography*: Tubal insufflation, originally described by Rubin, has probably been the greatest single advance in the diagnosis and treatment of sterility in the female. I have used both carbon dioxide and filtered air, and must frankly state that I have found no difference in the use of either, the patient's reaction depending entirely on the amount insufflated and not on the agent used. I have found the Jarcho Pressometer eminently satisfactory for tubal insufflation.

It need hardly be emphasized that the test should be done within four or five days after the cessation of menstruation. Also that, under normal conditions, the gas passes through the oviducts at a pressure between 60 and 80 mm. of mercury. The rate of increase in pressure should be gradual to avoid spasm of the tubal musculature. The diagnosis of blocked oviducts should not be made definitely until insufflation has failed on three or four occasions, at the same or different sittings. It is probably unwise to carry the pressure beyond 200 mm., though I have seen no ill effects from exceeding this figure on a number of occasions.

Though most authors on the subject insist that the injection of radiopaque substances should be reserved for those cases of apparently stenosed tubes, for purposes of localization, I am quite sure that the use of such substances has a therapeutic value in some cases. Any ill effects from the use of lipiodol or similar oily preparations I have yet to encounter, and within recent years their use has been employed almost routinely in my own practice. The number of cases in whom tubal insufflation failed to bring about the desired results, yet became pregnant following shortly upon the injection of lipiodol, has been rather convincing of its value therapeutically. Also, the information obtained with respect to the location of the block, and the likelihood of success or failure of plastic operations on the tubes supports, to some extent at least, the value of the procedure. The use of supposedly less irritating substances such as Visco-Rayopaque of "Roche" has been advocated by various investigators, but I have had no experience with such to date.

Summary and Conclusions

The factors most commonly encountered in my own series of cases were more or less in order of frequency: cervical erosions and infections, mild degrees of cervical stenosis, hypothyroidism, tubal occlusion, and impaired quality of spermatozoa.

First office visit: A complete medical and gynecologic history is taken, followed by a complete physical examination with special reference to the pelvis. The cervical canal is probed.

A notation of the husband's health, age, habits, etc., are made. Blood serology on both should be done.

Instruction is given her how to take vaginal or rectal temperature. A chart recording this temperature, the menstrual cycle, and dates of coitus is explained and given to her to keep her own record for at least two cycles.

The husband's sperm analysis should be done before the next visit.

Treatment of vaginal discharges of known etiology is advised.

Second visit: If the above records and laboratory reports are satisfactory, a basal metabolic test, tubal insufflation, and, where indicated, uterotubograms are done. If the tubes are patent, she is instructed about the Hühner test.

Third visit: Examination is made of the semen from the vaginal pool and the cervix within one of two hours of coitus, at the expected time of ovulation.

Erosion of the cervix, endocervicitis, etc., are treated when indicated.

The completeness of one's investigation in each case will naturally vary somewhat with the findings. Where absolute sterility is found, further investigation is discontinued.

Our results in overcoming sterility will improve when we are prepared to investigate the infertility of both husband and wife, and not the wife alone. The cooperation of both is necessary.

The survey necessary for the complete investigation of both male and female partners has been presented. Where any abnormality in the male exists, he should be referred to a competent urologist or internist for further study.

The future program may necessitate repetition of doubtful tests.

Six months should be sufficient time to investigate an average case. When all diagnostic data have been correlated, the cause or causes for the sterile mating should be explained to the patients and the prognosis outlined on the basis of established methods of correction and treatment. Where specific treatment is being carried out, a longer time than this may be necessary to justify it. Patients quickly lose interest in their study if they are advised to return in six months or a year, following each bit of investigation carried out.

Physicians, in general, should heed the solicitations of the sterile couple, and, if not interested, should refer them to someone who is. Such patients are usually sincere in their quest, almost always cooperative, extremely grateful when success is achieved, and most deserving of careful investigation and patient study.

ciated with sterility. It is routine procedure with me, in all cases being investigated, to have basal metabolic determinations made, and where variations from the normal spermanalysis exist, to have the husband done also. It is my own feeling that any apparently healthy individual in the minus bracket properly belongs in this hypothyroid group, and that a rate as low as (-7) to (-10), which we have been taught to consider within normal limits, is not so justified. Hypothyroid patients, even of mild degree, respond remarkably well to replacement therapy, and a few dollars' worth of thyroid will often pay dividends far in excess of many times this amount spent for more elaborate forms of therapy and investigation.

Some authorities mention the desirability of blood cholesterol determination, sugar tolerance tests, x-ray of the sella turcica, etc., but I feel they are not often indicated, and rarely offer much help.

Is there a psychologic factor in some cases? We all know of women infertile for years with no obvious reason quickly becoming pregnant following the adoption of a child. I can offer no scientific explanation.

Although it was not intended to discuss treatment in this paper, one should not merely mention endocrine investigation and leave it entirely at that. I am convinced that an appalling amount of time and energy expended in the past ten years or more in the indiscriminate use of sex hormone therapy in cases of sterility sometimes is unwarranted with harmful results.

Endocrine treatment of infertility in the female may be classified as follows: (1) treatment directed at correcting disturbances of endocrine glands which indirectly affect the reproductive processes; (2) treatment directed at correcting disturbances intrinsic in the ovary or uterus.

Siegler¹³ states that "in specific treatment the first factor to be considered is whether or not follicle maturation, ovulation, and its sequelae are properly taking place, and therapy should be individualized and cautiously and judiciously applied." He likewise states the necessity of determining which gland or glands are at fault, following which to administer the proper hormone in potent form, in adequate dosage, and over a sufficiently long time. One must remember, however, that excessive therapy eventually results in atrophy of the tissue which produces the hormone administered.

For my own part, except in cases of true genital hypoplasia, and the occasional case of irregular menstrual flow, which thyroid does not correct, female sex hormone is rarely used. In cases, however, where biopsy indicates lack of proper endometrial development, or where pregnandiol assays indicate lowered excretion (i.e., less than 35 mg. in the normal ten to twelve days), large doses of corpus luteum hormone should be tried. Henry¹⁴ apparently found it helpful in selected types of his so-called functionally sterile group. Hamblen¹⁵ covers this aspect of the subject in a masterly way in a recent publication.

Further details of treatment such as plastic operations on blocked tubes in selected cases, or operations on the male to correct aspermia or artificial insemination do not fall within the limits of this presentation.

AN IMPROVED OPERATIVE TECHNIQUE FOR SALPINGOSTOMY*

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THE operation of salpingostomy whenever tubal occlusion exists is justifiable only when the patient insists on having a child. It is taken for granted that the husband is healthy and fertile. It is also taken for granted that at least two or three previous insufflations have been unsuccessful.

Obstruction in the Fallopian tubes may be present anywhere throughout the lumen. When it occurs at the uterine end, intrauterine tubal implantation is necessary to restore patency. I believe it is the feeling of most gynecologists that this is rarely a justifiable procedure. It does not appear to be surgically or anatomically sound. Salpingostomy, on the other hand, offers possibilities.

Previous to September, 1943, other methods had been attempted by me with no resulting pregnancies. The present technique was suggested when, in the first patient to be reported, a radical operation was about to be begun a few minutes after an unsuccessful insufflation. As the tubes were being handled preparatory to their removal, the striking distention and crepitus suggested a salpingostomy, even if in view of previous experience this operation seemed a forlorn hope.

Since 1943 I have performed salpingostomy three times by this method and, although it seems fantastic, in each case pregnancy followed within a year.

The Operation

The anesthetized patient is placed in the lithotomy position, and one more insufflation is attempted to determine the patency of the tubes. Air is forced into the uterine cavity, and maintained at a pressure of 225 mm. of mercury for two minutes. The intrauterine instrument, if this final test fails, is withdrawn, the patient changed to the Trendelenburg position, and the abdomen opened. Occasionally it is found that the diseased tubes are so irreparably ruined by the previous pathologic process that nothing in the way of a reconstructive operation is possible. However, more often, on palpating the tubes, crepitus will be obtained in one or both, proximal to the "block" which obstructed the distal flow of the air when insufflation was attempted a few minutes before. Even when the tubes are enormously distended as they are in hydrosalpinx, the crepitation is very distinctly palpable to the point of occlusion. At any rate, the practical point is this—that if the tube is incised along its free border at the point of maximum crepitation, a new ostium can be established. When this is performed, a mixture of air and "tubal content" debris gushes forth. As in

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

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Discussion

DR. MARION HILLIARD, Toronto.—I agree entirely with Dr. Grant's presentation of his investigation, organizing it into three major visits of the patient, one of them being in the hospital. It is difficult to rule out a great many patients who just want to see if they are normal. I have found that 33½ per cent of the patients do not return when they find that a complete investigation is necessary both for themselves and their husbands. In my practice I send all the husbands to a urologist who is interested in this type of investigation and treatment.

I have found the use of Hodge pessaries of great value in cases of retroversion of the uterus, and would like to mention that these pessaries are good in cases of acute antelexion when the cervix is well up in front.

In a discussion of the relative diagnostic values of the Rubin test versus hysterosalpingograms, I have found it possible to put oil through the tube when it was impossible to be sure that air had gone through. Therefore, I would feel that a hysterosalpingogram would be necessary before an absolute diagnosis of sterility could be made. On the other hand, wherever there is any other gynecologic complaint such as intermenstrual discharge, dysmenorrhea, or profuse periods, a dilatation and curettage with the insufflation of tubes will have good therapeutic effect. I use hysterosalpingograms almost entirely and find them very successful. In a series of eighty-four cases, sixteen showed definite abnormalities without any previous histories of any gynecologic complaint or operative interference.

As to the use of thyroid, I agree with Dr. Grant entirely. I put my patients on one grain of thyroid daily, if the basal metabolism rate is not over plus six or seven. There has been some discussion as to whether this may not depress the normal thyroid function, if given over a period of time.

DR. GERIN-LAJOIE, Montreal.—I would like to stress that in our clinic we seldom do an insufflation test. We always use uterosalpingography with lipiodol with better results. We use it not only for sterility but for other diseases where it might be beneficial for the diagnosis. I would like to suggest the removal of the speculum before taking uterosalpingographs as advisable, for there might be findings which would be obscured.

probes, bristles, etc., into the uterine cavity. These procedures, involving as they do needless intratubal trauma are to be condemned. The gush of air when the scalpel opens the lumen is ample proof that the tube is patent, as far as the site selected for salpingostomy (See Fig. 1, *A*, *B*, and *C*).

Case Reports

CASE 1.—Mrs. W., aged 28 years, was seen on Sept. 4, 1943. At 19 years of age she had married, and gave a history of pelvic inflammation following the mating. During the past four years, numerous attempts at insufflation were negative, and she had been told that her tubes were "blocked." On Sept. 17, 1943, a final testing was carried out. The pressure was raised to 225 mm. and kept constant for two minutes. The tubes were found to be closed. The abdomen was opened. The right tube showed the characteristic ravages of pelvic inflammation, and was in the quiescent state of hydrosalpinx. It was impossible to find any semblance of a natural ostium. A new one was fashioned over a suitable spot where the adhesions were least dense, and where crepitation was most easily elicited.

The left tube appeared edematous, and air had traveled along its lumen to its middle third. The outer third was bound down tightly to the sigmoid colon. A salpingostomy was done on this tube by slitting it along its free border at the spot of maximum crepitation. The abdomen was closed. The convalescence was uneventful. Ten months after the operation I received a letter from her physician stating that she had unfortunately miscarried in the midtrimester of a pregnancy.

CASE 2.—Mrs. G., aged 28 years, was seen on June 12, 1944. This patient had been married for four years. A history of painful menorrhagia antedated her marriage. The pelvic findings were as follows. A retroverted, large, fixed uterus, with small bilateral masses. The cervix was clean. A tentative diagnosis of endometriosis was made. Previous tubal insufflations had been pronounced negative. Under anesthesia, a final testing was done. The tubes were closed. On opening the abdomen the diagnosis of endometriosis was confirmed. The right tube was occluded throughout the whole lumen, at least, there was no proof of air having passed as no crepitation was obtained.

The left tube and ovary were "dug out" of the pouch of Douglas. The tube was engorged with air as far as its distal third, and the fimbriated end was densely adherent to the ovary. A new ostium was fashioned over the free border of this tube at the point of maximum crepitation. The uterus was then suspended and the appendix removed. The convalescence was uneventful. The following year she conceived, and unfortunately miscarried. On Oct. 5, 1946, Dr. Adamson of Hamilton delivered her of a living female child.

CASE 3.—Mrs. M., aged 25 years, was seen on Sept. 3, 1944. This patient had been married for five years. Previously she had been operated upon by a general surgeon for pelvic inflammation, and the appendix, the right ovary, and part of the right tube removed. The menses were regular and painless. On Oct. 21, 1944, a routine insufflation of the tubes was done, and it was found that the air at a steady pressure of 225 mm. of mercury failed to pass into the peritoneal cavity. The abdomen was then opened. The remaining part of the right tube was very distended, and "crackled" on palpation. It was about three-fourths inch long, and clothed with dense adhesions. After freeing the minimum of adhesions necessary to make the plastic change feasible, a curved half-moon incision was made over the free border and this was deepened until air and tubal debris oozed forth. A new orifice was fashioned using interrupted sutures of fine chromic surgical gut on an atraumatic needle.

these patients the insufflated tubal wall is thin and avascular usually, the bleeding is slight. This absence of troublesome bleeding is invaluable. For one of the dangers heretofore in salpingostomy was the formation of a hematoma during the fashioning of the new ostium. This, together with the adhesions which usually followed in its wake, invalidated the future success of the operation.

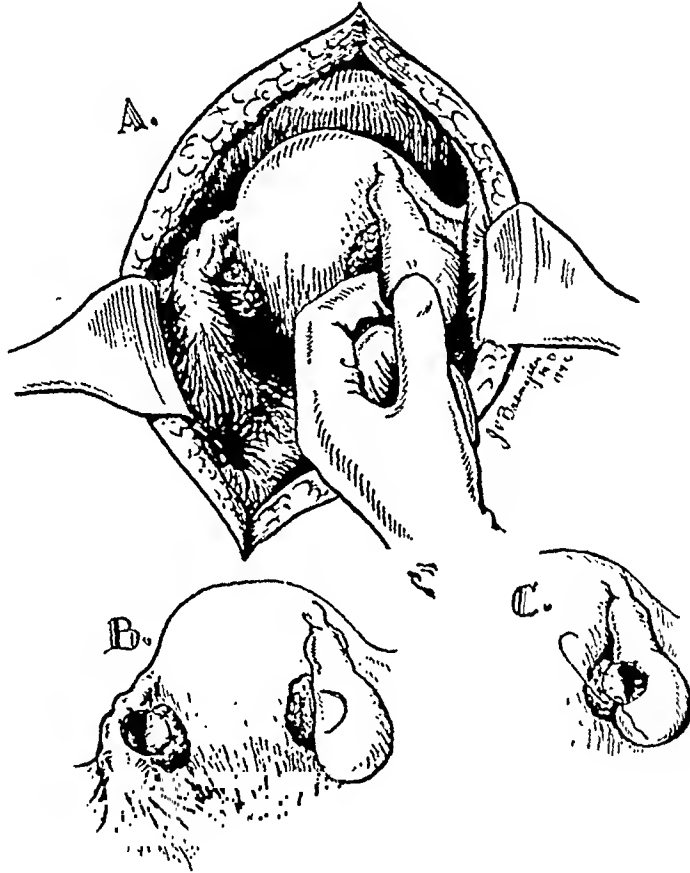


Fig. 1.—A, Exploring the abdomen and examining the Fallopian tubes. The tubes are closed. The patient has suffered from pelvic inflammation. The left hand of the surgeon is palpating the right tube. Over the area of maximum crepitation a new ostium will be fashioned.

B, Salpingostomy of the left tube. A curved incision (half-moon) opens the tube. This "trap-door" type of flap leaves a gaping wound, and there is very little chance of the ostium closing. The blood supply to the flap is preserved so that sloughing will not occur. By suturing it down to the ovarian hilum (which is practically avascular) every opportunity is given the ovum to tumble into the gaping mouth of the artificial ostium. The curved line on the right tube delineates the site of the incision.

C, Salpingostomy of the right tube. The flap is being sutured to the hilum of the ovary with fine chromic surgical gut on a small atraumatic needle.

The fashioning of the ostium may be left to the ingenuity of the surgeon. Fine silk or fine surgical gut on an atraumatic needle is advised. Any unnecessary separation of adhesions is to be avoided. Adhesions tend to reform. If it is possible to establish the artificial opening near the ovary, this should be done, but it should be remembered that the adnexa resent rough handling, and show their resentment in the form of troublesome oozing. As mentioned above, this may defeat the purpose of the operation. Nor is it necessary in this procedure to test the patency of the tubes from above by attempting to pass air, fluids.

A STUDY OF BREECH DELIVERY*

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(From The Vancouver General Hospital)

THE serious infant mortality associated with breech presentation is emphasized in all standard texts of obstetrics, the total uncorrected fetal death rate being placed at about 20 per cent. Stander states that approximately one-third of this loss is directly due to the presentation itself, while Holmes and Evans give the mortality for the child as 10 per cent. As suggested by Tompkins and others, it seems likely that the fetal risk has been exaggerated in the minds of obstetricians by the failure to distinguish between the infantile death rate associated with breech presentation and the mortality of breech delivery per se. The fact that the presentation is frequently associated with prematurity, placenta previa and fetal abnormalities must be borne in mind; all conditions carrying an inherent serious risk to the child.

Furthermore, statistics on breech delivery as published from large clinics are undoubtedly influenced by the fact that a considerable percentage of deliveries by interns in training is included.

Recent studies to determine the intrinsic risk of breech delivery present a more cheerful view of the picture. Hansen has collected a series of 112 consecutive cases from private practice with a corrected fetal mortality rate of 0.8 per cent. External version was not practiced, and the conduct of labor and delivery was most conservative. Tompkins has presented a series of 211 breech cases delivered by a group of 17 obstetricians in Philadelphia, all diplomates of the American Board of Obstetrics and Gynecology, with a corrected mortality rate of only 2.7 per cent. Perhaps the most striking results are those of Greig, who reports sixty personally delivered cases of breech presentation in primigravidas with but one stillbirth and no neonatal deaths. His method of delivery is extremely conservative, spontaneous birth with a minimum of manual assistance being the rule. Local (pudendal block) anesthesia was used, his recent cases having received no general anesthetic even for delivery of the head. Greig believes that fully 90 per cent of breech deliveries in primiparas can be spontaneous.

While admittedly these excellent results are reported by skilled obstetricians, it should be noted that in the conservative management, as recommended by Hansen and Greig, success depends more upon method than on manual dexterity, and that a similar technique therefore may be followed with considerable assurance, even by the neophyte in obstetrics.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

The left tube was now examined and found to be a typical hydrosalpinx with a closed fimbriated end. It had become enormously distended with air as a result of the attempted insufflation. The closed tube was separated from the outer pole of the ovary, and salpingostomy was performed simply by removing the distal part by circular amputation. On Dec. 20, 1945 (thirteen months after the operation), I delivered this woman of a living male child weighing 8 pounds 3 ounces.

Summary

Salpingostomy is justifiable in certain cases. It is admitted that the operation has a limited field of usefulness. A technique is described in which preparatory to laparotomy, air is forced into the uterus at a high pressure, and salpingostomy is then performed on the tube over the area of maximum crepitation.

Only three cases are reported, but the successful results seem to indicate the value of the method.

Discussion

DR. VAN WYCK, Toronto, Canada.—A review of the subject of plastic operations on the tube for the cure of sterility has not given a very favorable picture. The reason is three-fold. The relatively few live babies achieved by these methods; the undue proportion of ectopic gestations resulting; and finally the complications which may from time to time follow any laparotomy.

Dr. Johnston has described a modification of technique in which he has utilized tubal insufflation: (1) To determine the point of obstruction. (2) To select the best operative site for fashioning a tubal ostium. The maintenance of the distention of the tube when the abdomen is opened, renders the operative site more avascular and the operation more practicable.

One cannot, in such a small series, draw many conclusions. One cannot, also, neglect the fortuitous. However, I should like to suggest one procedure which might be added to his method. The preliminary lipiodol salpingography might still further eliminate those cases where plastic operation might give no reasonable hope of success.

TABLE II. FETAL RESULTS IN BREECH DELIVERY. VANCOUVER GENERAL HOSPITAL GROUP
(JAN. 1, 1945, TO JULY 1, 1946)

| NUMBER | STILLBIRTHS | NEONATAL DEATHS | FETAL MORTALITY |
|--|-------------------------------------|----------------------|-----------------|
| 145 | 7 | 1 | 5.5% |
| | <i>Personal Group (1935 Onward)</i> | | |
| 55 | 1 | 1 (Congenital heart) | 3.6% |
| | | Corrected | 1.8% |
| (Premature babies of less than 2,500 Gm., twins, and gross monstrosities excluded) | | | |

There was no maternal mortality in the entire series.

The Management of the Patient

Granting the conclusion that fetal mortality is largely dependent upon the success or failure to achieve a spontaneous or nearly spontaneous delivery of the breech, the conduct of labor is directed to this end throughout. The procedure as described is chiefly applicable to delivery in primiparas, and is modified as necessary in multiparas.

To avoid unnecessary worry, the expectant mother with a breech presentation need not be informed of the fact before labor commences. If she is aware of it, the importance of the condition is not emphasized. However, when labor is established, it is well to acquaint her of the situation, and to enlist her aid for the delivery to come. One explains that since her active cooperation in the birth will be required, she will not receive deep analgesia or amnesia. To this end such drugs as paraldehyde, scopolamine, and the barbiturates in high dosage, which tend to cloud the sensorium and produce restlessness, are contraindicated. However, since uterine inertia is not uncommon, the patient is protected against exhaustion and dehydration by adequate sedation and fluid administration.

TABLE III. DETAILS OF PERSONAL SERIES

| | | |
|---------------------|--------------------------------|----|
| A. Number of Cases | | 60 |
| | Primiparas | 42 |
| | Multiparas | 18 |
| | Average age of Primiparas | 27 |
| B. Type of Delivery | | |
| | 1. Spontaneous with manual aid | 43 |
| | 2. Extraction | 12 |
| | 3. Cesarean section | 5 |
| | 4. Forceps to aftercoming head | 18 |

When the cervix is believed to be fully dilated, the patient is prepared as for delivery, and a vaginal examination made to rule out the possibility of a prolapsed cord and to satisfy oneself that there is no remaining rim of the cervix. Not infrequently, and especially in footling presentations, the leading part may be visible at the vulva before cervical dilatation is complete. Premature expulsive efforts in such instances may result in the cervical rim offering obstruction to the aftercoming head. Sufficient time should be allowed to ensure that the cervix is not only completely dilated, but also "paralysed," as someone has aptly expressed it.

When we consider the effect of a more radical policy of delivery, namely elective breech extraction upon complete dilatation of the cervix, the fetal results are not comparable. Even in expert hands, the procedure is associated with a reported mortality for the child of from 6 to 10 per cent, although Goethals did succeed in achieving a mortality rate of 2.3 per cent in one series. Obviously, should the practice of elective extraction become widely adopted, the loss would be much greater. In an analysis of over 3,000 breech deliveries in the borough of Brooklyn, Gordon showed a fetal death rate of 18.7 per cent following extraction.

Material

A personal series of sixty consecutive cases of primary breech presentation, fifty-five of which were delivered vaginally, is presented as a further evidence of the benefits of a conservative policy in management. There were thirty-seven primiparas in the latter group. Since the purpose of the study was to determine the essential hazard to the child solely as a result of breech delivery, it does not include premature babies of less than 2,500 Gm. in weight. As emphasized by Beck and Philpott, the risk to premature infants in breech delivery is considerable because of the relative disparity in the diameters of the body and head. However, since maternal toxemia, atelectasis, and other conditions incident to prematurity may be associated, it is often difficult to determine exactly the deciding factor in the fetal mortality. Twin babies were excluded, since the second twin, when presenting by the breech, has its passageway already prepared. Gross monstrosities incompatible with continuing fetal life are excluded. Otherwise, the group represents the writer's total experience with breech delivery in private practice extending over a period of ten years. Cases of internal podalic version and extraction not being primary breech presentations are omitted. It has been the general policy (especially in the earlier years of practice) to make at least one attempt at external version when a breech was discovered during antenatal examination, otherwise this small series would have been considerably larger. In a few instances, however, the discovery of the presentation came as a surprise when the mother was seen in early labor. As it stands, the series reflects the experience of an average obstetrician in private practice following a definite plan of noninterference in labor in so far as possible. That an element of good fortune may have been associated with the results is freely admitted, and it is quite possible that a larger experience may show a higher fetal mortality rate.

Because of its small size, the personal study is supplemented by a similar review of the uncomplicated breech deliveries occurring consecutively in the Vancouver General Hospital from Jan. 1, 1945, to June 30, 1946, inclusive.

TABLE I. INCIDENCE OF BREECH CASES AT VANCOUVER GENERAL HOSPITAL
(JAN. 1, 1945, TO JULY 1, 1946)

| | |
|--|-------------|
| 1. Viable births | 5987 |
| 2. Total breech cases | 224 or 3.8% |
| 3. Uncomplicated breech deliveries | 145 or 2.6% |
| (Twins, monstrosities, less than 2,500 Gm. excluded) | |

While many of the cases in the latter series were delivered by specialist members of the attending staff, fully 60 per cent of them were under the care of various general practitioners of the visiting staff or were delivered by interns in training. The over-all group is, I believe, sufficiently large to indicate the general character of the fetal results in breech delivery at the Vancouver General Hospital.

The outcome for the child in the two series is shown in Table II.

In guiding the head through the pelvis the widest available diameters as determined by x-ray pelvimetry should be considered. I have had no experience with the Burns-Marshall technique of allowing the child to hang by the head so as to draw it into the pelvic cavity, but its enthusiastic recommendation by British obstetricians would suggest its use when necessary.

In delivery of the shoulders, arms, or head, I am convinced that it is a mistake to adhere rigidly to a planned routine in the face of an apparently conflicting mechanism. One must adapt the procedure according to circumstance.

Discussion

Many talks with younger practitioners on the subject of breech presentation has led me to the conclusion that there exists a considerable fear of the "breech birth" in the mind of the profession at large based upon the serious prognosis for the child. This exaggerated dread may express itself by too strenuous attempts at external version, by excessive haste or roughness in delivery, or by a frequent recourse to cesarean section.

The merits of external version when gently performed have been repeatedly attested, and it is far from my intention to question its value. Nevertheless, it is often most difficult of accomplishment, in the very instances where it would be highly desirable, namely, in primiparas where not infrequently a tense abdominal wall or engagement of the breech may prevent its performance. It would seem that the hazard of breech delivery is not sufficiently great to justify too vigorous or persistent attempts at external version in difficult instances, nor in particular to warrant its employment under anesthesia. An increasing number of cases of placental separation and other accidents are being reported.

The pharmacologic method of version during pregnancy by means of purgation as recommended by certain Spanish-American obstetricians is interesting and harmless and deserves more widespread clinical trial.

When we consider cesarean section, it is apparent that abdominal delivery must have wider application in breech presentation than in vertex cases. Since disproportion may not become evident until the aftercoming head reaches the midpelvis, trial labor is of little value. There is, moreover, no time for head molding. Careful clinical and radiologic examination of the maternal pelvis should generally indicate the way to safety. Even with the normal pelvis, the hazard to the overlarge child (of more than 4,000 Gm.) is to be remembered, especially in elderly primiparas. However, breech presentation as such should not be considered an indication for cesarean section except when the pelvis is contracted or under other unusual circumstances.

In this connection it is well to re-evaluate the slow labor in primiparas after a test of from twelve to eighteen hours. Ineffectual uterine contractions with a prolonged and that the risk to the child will be increased proportionately. thick, slowly dilating cervix will generally indicate that the labor will be unduly. Delivery by cesarean section may be the best solution in some of these cases.

Summary and Conclusions

Belief is expressed that a more favorable fetal mortality rate than generally quoted is possible, based upon the following considerations:

TABLE IV. DETAILS OF PERSONAL SERIES

| | | |
|-------------------------------------|-----------|--|
| C. <i>Average Duration of Labor</i> | | |
| Primiparas | 20 hours | |
| Multiparas | 6 hours | |
| D. <i>Average Weight of Child</i> | | |
| For Primiparas | 3,342 Gm. | |
| For Multiparas | 3,516 Gm. | |
| E. <i>Greatest Weight of Child</i> | | |
| For Primiparas | 4,290 Gm. | |
| For Multiparas | 4,050 Gm. | |

TABLE V. PERSONAL BREECH CASES DELIVERED BY CESAREAN SECTION

| NO. | AGE | PARA | PELVIS | X-RAY | TRIAL LABOR | WEIGHT OF CHILD | REMARKS |
|-----|-----|------|----------------------|-------|----------------|--------------------|------------------------------------|
| 1. | 25 | 0 | Android | Yes | None | 3,010 Gm. | Marked contraction of midpelvis |
| 2. | 27 | 0 | Gen. con- tracted | Yes | None | 3,150 Gm. | ----- |
| 3. | 27 | 0 | Android | Yes | None | 3,460 Gm. | Very small outlet |
| 4. | 32 | 0 | Android | Yes | None | 2,965 Gm. | Small mid-pelvis |
| 5. | 33 | 0 | Normal | Yes | 24 hours | 3.655 Gm. | Cervical dystocia |

Careful and frequent auscultation of the fetal heart is practiced throughout the second stage of labor so that an immediate extraction may be undertaken should fetal distress appear. If this precaution is observed, the stage of expulsion may be extended beyond the traditional two or two and one-half hours without anxiety if progress is being made. A too prolonged second stage, however, may favor the development of a contraction ring. The practice of "breaking up the breech" by bringing down a foot by Pinard's maneuver was rarely followed, it being considered preferable to perform complete extraction under full anesthesia if failure of advance occurred in the second stage of labor with the breech high.

When the perineum becomes distended, a pudendal nerve block anesthesia is induced using 1 per cent procaine solution containing three minims of epinephrine to the ounce. In a few minutes the pelvic floor may be painlessly dilated, if desired, by the familiar "ironing-out" maneuver. A wide episiotomy is then made, following which descent and delivery of the breech usually occur promptly. After the birth of the umbilicus, complete general anesthesia is induced and the anesthetic agent must act rapidly. A slowly acting anesthetic such as ether may be worse than none. As the anterior scapula presents, it is pushed toward the fetal spine as recommended by Potter, thus delivering the anterior arm. Should the anterior shoulder not appear promptly or the anterior arm be extended, the child's body is drawn slightly downward and rotated so as to make the posterior shoulder become anterior by the method so well described by Lövssett, though probably practised by obstetricians for many years. The rotation is then reversed to deliver the other arm. One trial is made to deliver the head by the modified Wigand-Martin maneuver. If easy delivery is not forthcoming, forceps are promptly applied. Whatever method is employed for the delivery of the head, flexion by jaw traction with rotation under the pubic arch is maintained so as to roll the head slowly out of the pelvis. General anesthesia is discontinued with the birth of the head, and the episiotomy repaired at leisure while the local anesthesia is still effective.

In his management Dr. Trites is conservative. The mother's forces are utilized to the full, and he interferes only when there is failure of progress. This wise restraint is the more admirable in that it calls for a minimum of general anesthesia and for no unusual dexterity on the part of the operator.

DR. WM. A. SCOTT, Toronto.—I do not use spinal anesthesia as a routine in obstetrics, but have adopted it to a greater extent than in the past. I use a low spinal anesthesia in all breech deliveries at or near term, and also when I anticipate a difficult operative delivery in a vertex presentation. The anesthetic need not extend to any great height, and it gives a relaxation of the soft tissues that facilitates all operative procedure.

I should like to ask Dr. Trites just what advantages a local, supplemented by a general anesthetic has over a low spinal anesthesia.

Dr. Trites laid down the dictum that a careful radiologic study of the pelvis would determine those cases where, because of pelvic disproportion a cesarean section is indicated. I would like his opinion on a somewhat controversial point. In an elderly primipara in whom there is no disproportion, with a breech presentation and extended legs, one anticipates a difficult delivery. Under such circumstances is one not justified in doing a cesarean section in the interests of the child?

DR. B. P. WATSON, New York.—We have for many years at the Sloane Hospital carried out a very conservative policy in breech delivery. Our teaching has been that practically every breech should deliver spontaneously. Full dilatation of the cervix and stretching of the pelvic floor is allowed to occur by the breech itself. The frank breech is not broken up unless descent is arrested.

The greatest aid in reducing fetal mortality is episiotomy. This should be done as soon as the breech begins to stretch the perineum. It should not be deferred until after the breech has been born and difficulty with the aftercoming head is encountered. When we follow these rules we do not fear a breech delivery anymore than we do a vertex.

DR. TRITES (Closing).—It was gratifying to note that Dr. Mitchell shares my feelings with respect to breech presentation, and I should like to congratulate him on his results. I have had no experience with the use of the Voorhees' bag in breech cases, but I believe that it might have a place when the cervix was dilated to 4 or 5 cm. and progress slow. Here it might be used to advantage.

In replying to Dr. Scott, I have had no experience with spinal anesthesia in delivery, but am assured that it gives excellent relaxation of the pelvic floor, and I believe it might be of special use in certain cases. The particular advantage of local anesthesia is that the patient may use her voluntary powers up to the time of actual delivery. There is also the question of the availability of trained anesthetists, which was until recently a constant difficulty in the hospital where I work. Dr. Scott mentioned the question of elective cesarean section in the elderly primipara with a frank breech presentation and a normal pelvis. It is quite true that the risk to the child may be increased because of the patient's age. In deciding on the method for delivery, I would be guided by two or three factors—first, the estimated size of the child, and secondly the condition of the cervix. If the cervix were soft and well effaced when labor commenced, the child not obviously overlarge, and the breech well engaged, I would give such a patient a test of labor to judge her progress with the thought that I could change my method of delivery at the end of twelve hours, if considered advisable.

Replying to Dr. Grant, his question is well taken regarding the necessity of "ironing-out" the perineum before delivery. One of the advantages of local anesthesia is that the pelvic floor will be relaxed, and in the average patient there will not be much need to do any ironing-out; although, at times it is helpful to do so when the patient has a rigid levator ani muscle.

I am grateful to Dr. Watson for his support of the conservative method of treatment, and agree fully that episiotomy should be done early, well in advance of the birth of the breech.

1. A complete study of the maternal pelvis by clinical and radiologic methods with delivery by cesarean section if the pelvis is contracted.
2. A conduct of labor designed to achieve a high incidence of spontaneous delivery of the breech with interference only on definite indication.
3. Constant personal supervision of the second stage of labor by the attending obstetrician.
4. The utilisation of local anesthesia, wide episiotomy, and frequent application of aftercoming head forceps in delivery.

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Discussion

DR. ROSS MITCHELL.—In his well-reasoned paper Dr. Trites shows that the prevalent gloom in breech presentation is unjustified, and that the risk to the fetus in primary breech presentations can be much less than is usually stated. Probably it is no greater, and may be even less than for occiput posterior positions. Personally, the latter have given greater worry than breech presentations.

The bugbear of disproportion can be obviated by careful clinical observation, supplemented when necessary with x-ray examination. The incidence of cesarean section need not be high. Dr. Trites presents from his own practice sixty consecutive cases of primary breech presentation with five abdominal deliveries. In my own practice from July 1, 1936, to the present date there were fifty-six cases of primary breech presentations at term or near term with two abdominal deliveries. The combined groups may be presented thus:

| <i>Method of Delivery</i> | | | |
|--|-----|--|----|
| Vaginal deliveries | 109 | Cesareans | 7 |
| <i>Vaginal Deliveries</i> | | | |
| Primiparas | 73 | Multiparas | 36 |
| <i>Fetal Mortality in Vaginal Delivery</i> | | | |
| Total | 109 | Stillbirths, 1 Neonatal Death,* 1 fetal mortality, 1.72% | |

In my own series of fifty-four deliveries there were four babies weighing 9 pounds 11 ounces; 9 pounds 10 ounces; 9 pounds 3 ounces; and 9 pounds 2 ounces, respectively, and a total of eight weighing 8½ pounds (3,800 Gm.) or over. The management of delivery was substantially that advocated by Dr. Trites. I can emphasize the value of local anesthesia, of deep episiotomy and of not hurrying the head through the birth canal.

*(Congenital heart) Corrected mortality 0.86 per cent.

A laparotomy was performed and the mass was found to be situated in the location of the right ovary and obviously containing the pregnancy. The omentum and small bowel were adherent to the mass. After freeing of adhesions the mass was seen connected to the uterus by the ovarian ligament, which was enlarged. The uterus was slightly enlarged, and retrodisplaced in the cul-de-sac. Both tubes were lying free and looked normal. The left ovary was cystic, about the size of a lemon, lying free in the left fossa. The right ovary containing the



Fig. 1.—Specimen opened showing surrounding capsule of ovarian tissue.

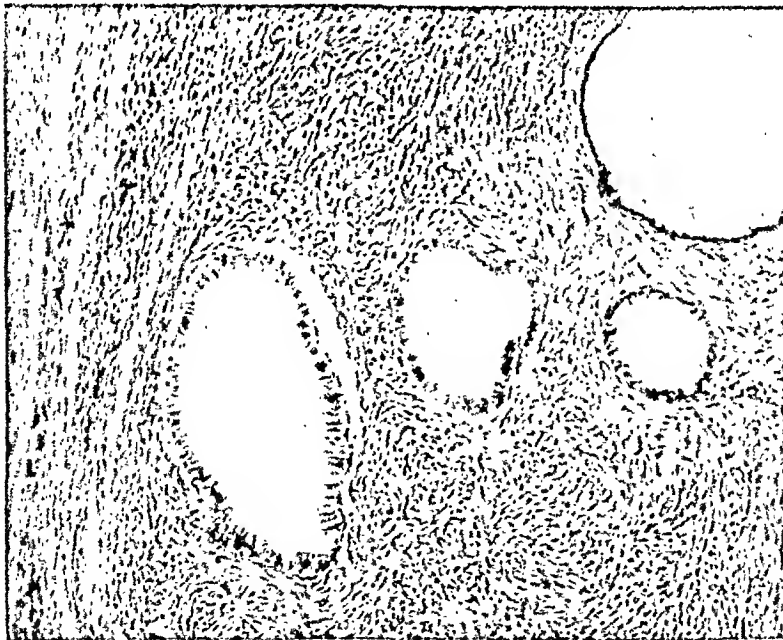


Fig. 2.—Section of capsule showing ovarian tissue and gland suggestive of endometrial glands.

pregnancy and the left ovary containing the cyst were removed. The post-operative course was uneventful, and she was discharged on the thirteenth day.

Pathologic Report.—The specimen consisted of a large ovarian tumor, measuring 19 by 13 by 9 cm., and weighing 1,300 grams. The external surface was smooth and glistening. On section, the tumor was found to contain a large fetus

OVARIAN PREGNANCY*

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MRS. I. M., a 42-year-old white female, entered the Hamilton General Hospital Sept. 17, 1945. At that time she complained of "no periods for twelve months."

Her last normal menstrual period was Sept. 1, 1944. She had slight nausea with occasional vomiting in October, 1944, which only lasted for approximately two weeks. She visited her doctor in November, 1944, at which time a diagnosis of pregnancy was made. She did not return as she felt perfectly well. She was never aware of any abdominal enlargement or pressure of abdominal mass, nor did she feel any fetal movements. She continued well until April, 1945, when she began to have pains around the level of the umbilicus accompanied by marked constipation, and "a lot of gas." This lasted for approximately one week, during which time she was very tired.

From the middle of May to the middle of June, 1945, she had intermittent spotting of blood from the vagina accompanied by small clots which lasted five days. There was no bleeding since that time. She had intermittent pain in the right lower quadrant for two weeks, which would disappear with rest.

In August, 1945, she was examined regarding accepting steady employment. At this time she was referred for x-ray examination of the abdomen. The report was as follows:

A film of the abdomen showed the presence of a single fetus of approximately five months. The midpoint of the head was at the level of the posterior iliac crest on the right side. There was overriding of the fetal skull bones, breech presenting, spine to the left. No placenta could be identified with any certainty as such, and the total mass was rather smaller than one would anticipate in consideration of the various elements contained in a pregnant uterus. No abdominal masses other than this pregnancy were identified.

Hospitalization was advised but she did not report for another month.

She had two previous normal pregnancies and deliveries twenty-four and twenty-two years ago.

No abnormalities were present until the onset of her present illness.

Physical examination on admission showed her blood pressure to be 124/82; temperature 98.2° F.; pulse 70; respiration 18; red blood cells, 5,400,000; white blood cells 8,000; hemoglobin 97 per cent.

Urinalysis and blood chemistry normal.

Examination essentially normal except for abdomen and pelvis.

There was a firm mass, size of football, rising from pelvis to just above level of umbilicus lying more to the right than to the left side. There was no tenderness, and the mass seemed partially moveable. The cervix was firm, elongated, and closed. It was thought that the uterus could be palpated in the cul-de-sac, and this mass was probably extrauterine.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

Original Communications

IN VITRO FERTILIZATION AND CLEAVAGE OF HUMAN OVARIAN EGGS*

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IN 1880, S. L. Schenk,¹ a Viennese embryologist, reported in some detail his experiments on in vitro fertilization of the ovarian eggs of the rabbit and the guinea pig. He described the first cleavage, as it occurred in vitro, and noted the inequality in size of the two resulting daughter cells. Some years later, Onanoff,² in a brief note published posthumously in 1893, mentioned that he had been able to induce in vitro fertilization and cleavage of uterine eggs of the rabbit and the guinea pig. He stated that the eggs had developed in vitro up to the eight-cell stage. Furthermore, this author reported that when ova fertilized in vitro were transferred to the abdominal cavity of another animal, whether male or female, of the same species, development continued until the embryos had attained the stage of the primitive streak. No details or photographs were furnished in connection with these experiments, nor has a careful survey of the literature discovered confirmation of these results by other investigators.

In 1930, Pineus³ observed sperm penetration in tubal rabbit eggs inseminated in vitro. By transplantation of such eggs into the oviduct of a pseudopregnant rabbit which subsequently produced young, possessing the proper genetic characteristics, Pineus and Enzmann⁴ in 1934 presented what they regarded as the "first certain demonstration that mammalian eggs can be fertilized in vitro." In the same year, Krassovskaja⁵ reported continuous observations for many hours of in vitro fertilized tubal rabbit eggs. Forty-six hours after spermatozoa had been added to the egg, this author noted the development of the morula stage (twenty-eight cells). Subsequently, this same investigator⁶ described in vitro fertilization and cleavage of tubal rabbit eggs that had been inseminated with rat spermatozoa.

In 1935, Pineus and Enzmann⁷ transplanted into the Fallopian tubes of pseudopregnant rabbits ovarian eggs that had been inseminated in vitro. Two to three days later, regular cleavage was observed to have occurred in a small number of cases. Consequently, these investigators concluded that "normal fertilization can be secured with eggs removed from the follicles." As a final proof that true fertilization of mammalian ovarian eggs can occur in vitro, Pineus⁸ in 1939 demonstrated that some ovarian rabbit eggs that had been exposed to spermatozoa in vitro possessed the diploid number of chromosomes.

Early cleavages in vitro have been observed in rabbit eggs that had been fertilized in vivo. Lewis and Gregory⁹ obtained cinematographs of such eggs as they developed from the one- to the eight-cell stage. In the guinea pig, Squier¹⁰ reported in vitro cleavage from the two- to the four-cell stage of four eggs that had been fertilized in vivo.

*This study has been aided by grants from the William F. Milton Fund of Harvard University, the Committee for Research in Problems of Sex, National Research Council, and the Carnegie Corporation of New York.

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measuring from vault to coccyx 21 centimeters. Lying at the opposite end of the tumor and just beside the fetus, to which it was joined by the umbilical cord, was a placenta measuring 10 by 5 centimeters. Both fetus and placenta were encapsulated by a very thin wall, the inner lining of which was fairly smooth. The average thickness of the wall was $1\frac{1}{2}$ millimeters. The fetus was well formed, and showed no gross abnormalities.

Sections of the other ovary which measured 6 by 5 by 4 cm. showed it to be cystic and thin-walled. It was found to be filled with clear serous fluid. The inner lining of the cyst was smooth and glistening. To one side could be seen a small portion of tissue which appeared to be atrophic ovarian tissue.



Fig. 3.—Section of capsule showing ovarian tissue and corpus albicans.

Microscopic.—Sections of the wall showed it to be composed of typical but compressed ovarian stroma containing a compressed corpus albicans. On the inner surface of one section could be seen numerous fragments of hairs embedded into the ovarian tissue. The surrounding tissue showed foreign body giant cell reaction. This portion of the wall unquestionably contained ovarian tissue. Repeated sections through the wall of the tumor showed the complete absence of epithelial lining and the constant presence of ovarian stroma. Some sections showed several glands lined by cuboidal and columnar epithelium. Sections of the other cyst showed it to be lined with very flattened epithelium which has ovarian stroma along one area.

Pathologic Diagnosis.—(1) Ovarian pregnancy, and (2) serous cyst of left ovary.

The patient was seen in the office six months later. She had had no bleeding since discharge from the hospital and was feeling well. Examination revealed nothing of note at this time.

It is felt this case meets all the criteria of true primary ovarian pregnancy.

similar stage, but part of the cytoplasm appeared fragmented, and soon proceeded to undergo rapid, degenerative changes. In this report, as in the preliminary one,²⁰ we will therefore confine our discussion to the two eggs in the two-cell stage and the more normal appearing of the two eggs in the three-cell stage.

The Two-Cell Stage of the Human Egg

First Specimen.—The first specimen was obtained from a 38-year-old married woman (No. 20,768) who had had four labors, and was admitted to the hospital with a diagnosis of relaxed perineum, lacerated, cystic, eroded cervix, and prolapse. At operation, on the tenth day of the cycle, a complete hysterectomy and right salpingo-oöphorectomy were performed. Cycles immediately preceding operation had been, respectively, twenty-seven, twenty-three, forty-seven, and twenty-eight days. The endometrium was found to be in the late proliferative stage.

The egg was recovered free in the follicular fluid drained from a bluish follicle, 2.3 cm. in diameter, in the extirpated right ovary, about one hour after oöphorectomy. When first observed, the ovum was within a moderate investment of granulosa cells. After rapid transfer through three portions of sterile Locke's solution, it was pipetted into a Carrel flask containing 3 c.c. of serum prepared from the blood of the egg donor.^{*} The blood had been taken from the patient after the operation. The egg was then placed in the incubator at 37.5° C. It had been at room temperature for about three hours; i.e., the time elapsing since oöphorectomy.

After twenty-seven hours of culture, the preparation was removed from the incubator and examined. The compact granulosal investment, which had surrounded the egg on the previous day, now appeared as a loose meshwork of shrunken, degenerated, granulosa cells. The egg was rapidly transferred through small amounts of Locke's solution in three watch glasses. In the third watch glass were then pipetted a few drops of the so-called "fertilizing suspension" of spermatozoa. This had been prepared as follows:

Seven-tenths of 1 c.c. of a semen specimen one and one-half hours old (in which 95 per cent of the spermatozoa were highly motile) was pipetted into a centrifuge tube and the volume brought to 2 c.c. with sterile Locke's solution. After being mixed, the suspension was centrifuged for fifteen minutes at full speed.[†] The supernatant fluid was then decanted, and to the firm white sediment was added Locke's solution, again to a volume of 2 c.c. The sediment was diffused in the medium by gently drawing the former in and out of a pipette. Centrifugalization and decantation were repeated, and then to the washed sediment was added Locke's solution to a volume of 0.2 c.c.; i.e., about one-third the original volume of the semen used. A hanging-drop of this suspension showed high concentration and activity. At the time when the spermatozoa were added to the egg, the former had been at room temperature for two hours and forty-five minutes; i.e., the interval since ejaculation.

The watch glass containing the ovum and spermatozoa was left on the stage of the dissecting microscope at room temperature for one hour, the egg being kept in constant view (at a magnification of $\times 35$). The spermatozoa showed great activity throughout the period of observation; they were clearly seen to travel through the interstices of the loose cellular formation surrounding the egg, and many were noted in active motion around the zona pellucida.

^{*}In all the experiments reported here, the serum used for culture of the eggs prior to exposure to spermatozoa was that of the patient who had furnished the eggs, while subsequent culture (following contact with spermatozoa) was carried out in serum of any patient willing to donate blood.

[†]About 3,500 revolutions per minute; an International Clinical Centrifuge with a No. 804 angle head was used.

In vitro insemination experiments have also been performed with eggs of the mouse and rat.^{11, 12} While certain effects of spermatozoal action were noted, such as dehiscence of follicle cells (in both mouse and rat eggs), as well as shrinkage in volume of the egg and second polar body formation (in the rat egg), cleavage was not reported in these studies.

In vitro cleavage of in vivo fertilized rat eggs was occasionally observed by Defrise¹³ when the eggs were cultivated in certain media. Only one or two divisions were noted. In their comprehensive monograph on the mouse ovum, Lewis and Wright¹⁴ include a photograph of an egg fertilized in vivo that divided into two cells in vitro.

To our knowledge, there have been no reports of in vitro fertilization of the eggs of higher mammals. In 1941, Lewis and Hartman¹⁵ mentioned two unsuccessful attempts to fertilize tubal monkey eggs in vitro. Previously, these same investigators¹⁶ had cultured in vitro from the two- to the eight-cell stage a monkey egg fertilized in vivo.

Most textbooks of embryology comment on our lack of knowledge of the fertilization and first cleavage stages of the human ovum. We have encountered in the literature only two references to the earliest stages of the human zygote. In 1944, Hamilton¹⁷ reported in a fresh tubal egg removed from an operative case the presence of many spermatozoa in the zona pellucida, and toward the center of the egg a clear area containing "dark rodlike bodies suggestive of chromosomes on the spindle of first cleavage." However, since this specimen was lost before fixation, there is no proof that the egg was actually fertilized. Shortly afterwards, Hamilton¹⁸ noted, in a fixed preparation of an unsegmented human tubal egg, many spermatozoa in the zona pellucida, and within the cytoplasm, two nuclei of unequal size, which he regarded as the pronuclei. This paper appeared in abstract form; so far, we have been unable to find a more detailed account.

In 1939, Pineus and Saunders¹⁹ reported that about 30 per cent of human ovarian ova cultured in blood serum for intervals ranging between eight and one-half and twenty-four hours showed polar body formation and hence became theoretically susceptible to fertilization. On the basis of these findings, we have made numerous attempts to initiate in vitro fertilization of human ovarian eggs cultured for varying lengths of time. Utilizing the surgical material available at the Free Hospital for Women, we performed most of our experiments on eggs from ovarian tissue removed just prior to the expected time of ovulation. Nearly 800 human follicular eggs have been isolated and studied during the course of this investigation; of these, 138 have been observed after exposure to spermatozoa in vitro.*

Several factors were varied through the period of this study; e.g., the conditions of culture of the eggs, both before and after exposure to spermatozoa, the duration of contact of egg and spermatozoa, and the concentration of the sperm suspensions used. Employing a certain combination of these variables, we have been able to induce cleavage in three experiments. A condensed report of these findings has been published previously.²⁰

In two of these cases (No. 20,768 and No. 14,518), the egg, after being subjected to certain procedures (to be described later), was found to be in the two-cell stage. In the third case (No. 21,012), two eggs divided. One of these, when first seen in cleavage, consisted of one large blastomere and two smaller ones, each of the three containing a round, vesicular body, which, at the time, we believed to be a nucleus. The second egg from this same patient was in a

*Most of the eggs studied were obtained by incising individual follicles, ranging in size from 3 mm. to about 3 cm. However, a few of the eggs were recovered by teasing pieces of ovarian tissue in a dish containing Locke's solution and allowing the ova to float into the surrounding fluid. The follicles from which these eggs originated were, as a rule, smaller than 3 mm. in diameter; in some cases, they were too small to be seen with the naked eye.

of cystocele, rectocele, and retroverted, prolapsed uterus. A complete hysterectomy and right salpingo-oöphorectomy were performed on the eleventh day of the cycle. The endometrium was in the late proliferative phase of its development. The last two cycles preceding operation had been, respectively, twenty-eight and thirty-four days long.

Twelve eggs were recovered from the extirpated right ovary by incising and flushing the follicles, and one from follicular fluid obtained by aspiration in situ of follicles of the left ovary. Since the follicles visible in the right ovary were closely approximated on the surface, it was not possible to identify the one from which any particular egg was derived. Although twelve eggs in all (one was lost) were carried through the entire procedure and exposed to the same technique, only one of them divided.

This ovum was one of a set of four, of which three, when first seen, were covered by a thick granulosa cell investment, and one by only a few rows of cells. The eggs were washed twice in Locke's solution, and were then transferred to a Carrel flask containing 3 c.c. of serum that had been prepared from blood taken from the egg donor twenty-two hours previously. The preparation was then placed in the incubator at 37.5° C. At this time, the eggs had been at room temperature for about three and one-half hours; i.e., the interval since oöphorectomy.

After twenty-two and one-half hours' incubation, the eggs were washed once in Locke's solution and exposed for two hours at room temperature to a sperm suspension prepared from the same donor and in essentially the same manner as in the first case reported above. At the time when the spermatozoa were added to the eggs, the former had been at room temperature for three hours; i.e., the interval since ejaculation. The ova were then washed twice in Locke's solution and transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that two hours previously had been given by a 62-year-old patient with carcinoma of the cervix uteri. The preparation was then incubated for forty-five hours at 37.5° C.

When examined at the end of the incubation period, the egg, as observed through the wall of the flask, was found to be in the two-cell stage. A photograph (Fig. 2A), made of the specimen two hours later, shows it to resemble very closely the first egg recovered in the same stage (Fig. 1A). Two "biscuit-

Fig. 1.—No. 20,768. Human egg in two-cell stage: *first specimen*. This egg was recovered free in the fluid drained from a 2.3 cm. ovarian follicle of a 38-year-old white woman after laparotomy on the tenth day of the cycle. After having been washed in Locke's solution, the ovum was cultured for twenty-seven hours at 37.5° C. in the serum of the same patient. It was again washed in Locke's solution and was exposed in vitro for one hour at room temperature to a washed concentrated suspension of human spermatozoa in Locke's solution. It was then transferred to serum from a 51-year-old female patient and incubated. After forty and one-half hours of culture, the egg was found to be in the two-cell stage, and a sketch was made of it. The specimen was then fixed, but was lost during dehydration.

A. Free-hand sketch of egg under high power of the compound microscope (after forty and one-half hours of culture).

B. Convuluted wall of mature Graafian follicle from which the egg was recovered. Insemination of the egg took place twenty-nine and one-half hours after the follicle wall was fixed. Section showing granulosa, theca interna, and theca externa. There is some focal separation (? artifactual) between the granulosa and the theca interna. In the theca interna, there is considerable vascularization and congestion. Note large, pale-staining cells of the theca interna, as contrasted with the small, polyhedral, dark-staining cells of the granulosa. Mitoses are seen in the theca interna, but not as frequently as in the granulosa cells. The theca externa cells are cylindric and stellate and are separated by variable amounts of edema fluid. It appears as though luteinization had just begun in the theca interna, but not in the granulosa cells. Fixed in Bouin's solution; embedded in paraffin; sections cut at 6 μ . and stained with hematoxylin and eosin. (X400.)

At the end of one hour, the ovum, along with some of the surrounding sperm suspension, was transferred to a Carrel flask containing 3 c.c. of serum of a 51-year-old patient who had been admitted to the hospital because of dysfunctional flowing. The blood had been obtained from the patient about six hours before the egg was placed in the serum. As the egg was pipetted into the Carrel flask, the loose formation of degenerated cells surrounding it suddenly dropped off, and it appeared as a single round cell with a fuzzy border.

When it had been cultured for forty and one-half hours, the ovum was washed out of the Carrel flask into a watch glass with Locke's solution.* In the plane of examination under the dissecting microscope, it now appeared to consist of two equal, spheroid blastomeres, each measuring 86μ in diameter, and was enclosed within a zona pellucida of uniform thickness, measuring 14μ .

A sketch of the egg was made under the compound microscope (Fig. 1A). Now the blastomeres appeared elliptic. At this time, a slight inequality in size of the blastomeres was noted. The ovum was then gradually fixed in Bouin's fluid by removing the surrounding medium (Locke's solution) and substituting the fixative, drop by drop. Fifteen minutes after the start of fixation, the ovum had undergone considerable shrinkage (to almost one-half its original volume). Dehydration had nearly been completed when the egg, unfortunately, was lost.

The Follicle Wall.—For several reasons, it seems worth while to include in this report a photomicrograph of the stained section of the follicle from which this egg was obtained (Fig. 1B). In the first place, it is the only one in our large collection of so-called "preovulatory" human follicles which we are certain contained a fertilizable ovum at the time the section was taken; i.e., it is the only section in existence, as far as we know, of a human ovarian follicle which can be exactly dated with respect to subsequent fertilization of the egg derived from it. The time interval between fixation of this follicle and insemination of the egg was twenty-nine and one-half hours.

In section, the convoluted wall of this follicle shows the three typical layers: granulosa, theca interna, and theca externa. The inner, or granulosa layer, is composed of small, polyhedral, dark-staining cells in which mitoses are prominent. The basal layer is more closely packed and the nuclei are more cylindric with their vertical axes arranged perpendicularly to the follicle wall. There is some focal separation (?artifactual) of the granulosa and theca interna. The latter is well vascularized, congested, and composed of cells which are larger, paler and more irregular than those of the granulosa. Mitoses are seen in the theca interna, but not as frequently as in the granulosa cells. The theca externa cells are cylindric or stellate and separated by variable amounts of edema fluid. It appears as though luteinization has just begun in the theca interna, but not within the granulosa cells. Apparently, then, this follicle represents a typical "preovulatory" stage; i.e., a mature follicle that is just about to rupture.†

Second Specimen.—Of the second egg in the two-cell stage we have a complete series of stained sections. Essentially the same procedure as described above was carried out on an ovum, washed from a follicle of a 31-year-old para vi, gravida viii (No. 14,518), who was admitted to the hospital with a diagnosis

*According to our usual technique, the eggs are pipetted out of the Carrel flask. In this case, however, it was not possible to identify the egg through the wall of the flask, as some contamination of the medium had occurred, probably due to the fact that in transferring the egg to the Carrel flask part of the sperm suspension had been carried along with it. Contamination of the medium was also noted in the third experiment to be described, where the same procedure was followed, but not in the second experiment. In the latter case, the egg was washed several times before transference to fresh serum.

†We are indebted to Doctor Arthur T. Hertig for this description of the histology of the follicle wall.

shaped"¹⁰ blastomeres of slightly unequal size, containing granular cytoplasm, are enclosed within the zona pellucida. Numerous spermatozoa are present, some along the border and at least one within the zona.

The entire egg (including the zona pellucida) measured 153μ by 155μ ; the vitellus was 100μ by 113μ , and the average thickness of the zona pellucida was 23μ . The blastomeres measured 88μ by 58μ , and 105μ by 58μ , respectively.¹

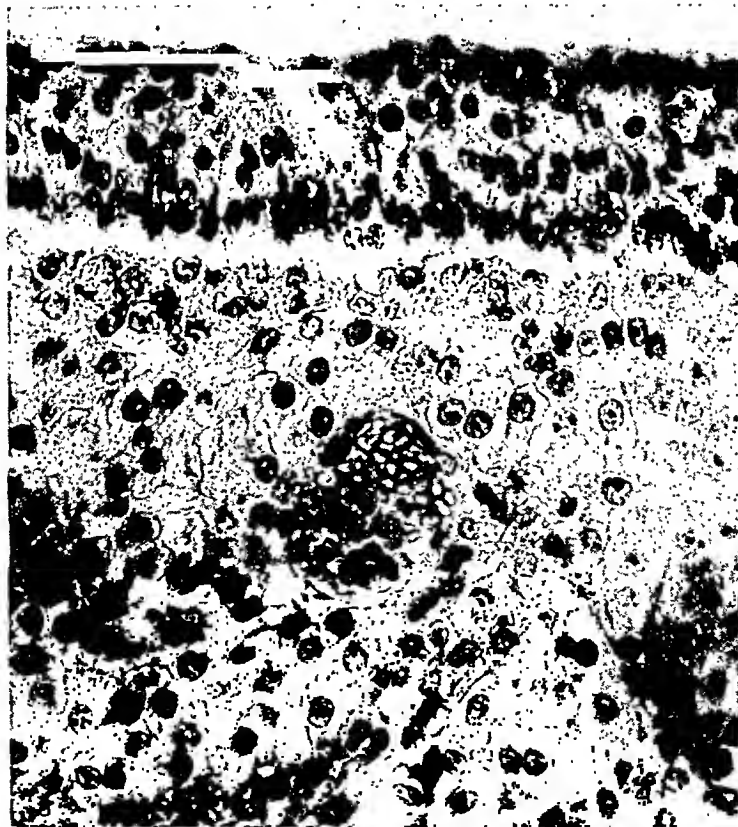
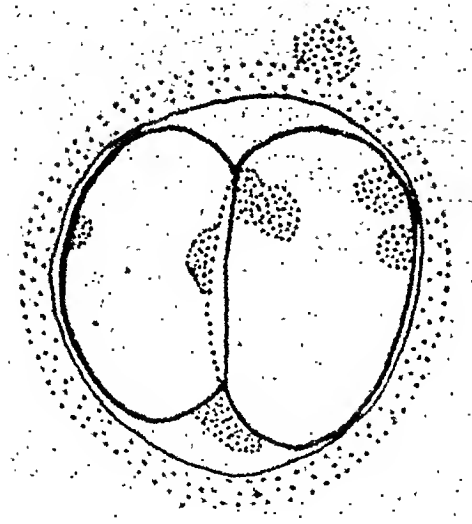
The egg, transferred to a plasma drop, was fixed according to the method described by Pincus.⁸ The plasma drop was warmed for one-half hour under an electric light bulb. The resulting clot was then carried through the double embedding celloidin-paraffin method, serially sectioned at 8μ , and stained with hematoxylin and eosin.

Since the ovum is included in eight sections, its total thickness after fixation is approximately 64μ . A section through the middle of the specimen (Fig. 2B) measures 50μ by 75μ (excluding the imperfect zona). The blastomeres (designated, for convenience as "A" and "B," from left to right) measure 63μ by 39μ , and 66μ by 36μ , respectively. The cytoplasm appears uniformly granular, with the exception of the polar regions where there is beginning vacuolization, as had been noted in the fresh specimen immediately following photography. In the approximate center of each cell, there is a round, vesicular nucleus containing a chromatin meshwork. The nucleus in blastomere "A" measures 18μ by 13μ , and that in blastomere "B," 16μ by 15μ . The zona pellucida surrounds the egg over about two-thirds of its circumference. Failure to retain the entire zona pellucida in section was doubtless due to the method of fixation; as seen in Fig. 2A, it had been intact in the fresh specimen. In a clearly defined portion (near "1 o'clock"), the zona measures 7μ to 8μ across. Several dark bodies suggestive of sperm heads may be identified on the photograph; one of them appears to be just within the cell body of blastomere "B" (near "1 o'clock").

The section adjacent to the one described above, and represented in Fig. 2C, was, unfortunately, torn during cutting and is reproduced only to show the polar body near "11 o'clock," beside blastomere "A." The polar body measures 18μ by 10μ , and contains what appears in the photograph as a group of chromatin units discrete enough to be counted. However, when the photograph is magnified twelve times, we see the chromatin in the form of a lobulated body, only two clumps being definitely separated from the general mass. Opposite blastomere "B" (at about "3 o'clock") two dark bodies resembling sperm heads are seen. Other sections of this egg show one, five, seven, and nine such bodies, respectively.

¹The so-called "biscuit" shape is characteristic of the blastomeres of other mammalian eggs in the two-cell stage.¹¹ Inequality of the daughter cells during early cleavages has been noted in the monkey egg,¹² as well as in the eggs of the rabbit and guinea-pig,¹ the rat,¹³ the mouse,¹⁴ and other mammals.¹⁵ The larger cell divides first, thus accounting for the occasional finding of an egg in the three-cell stage, as shown in Fig. 3.

²In both this specimen and in that of the three-cell stage (to be described below), the sum of the dimensions of the individual components of the egg in each diameter, as listed, does not equal the dimensions of the egg as a whole in that particular diameter. There are two reasons for this discrepancy. First, the measurements in each diameter of the vitellus and of the individual blastomeres were taken through their respective centers, rather than through the middle of the egg as a whole; i.e., along a slightly different axis. This was done in order to compare the dimensions of the fresh with the fixed preparation of each egg; in neither of the fixed preparations was the egg surrounded by an intact zona. The numerical discrepancy noted here is also due in part to the presence of a shrinkage space (perivitelline space) between the vitellus and the zona. The failure of the vitellus to fill the entire zonal cavity is characteristic of other mammalian eggs after ovulation.¹⁶



B.

Fig. 1.—(See legend on opposite page.)

The entire egg (including the zona pellucida) measured 170μ by 183μ ; the vitellus was 103μ by 127μ , and the zona pellucida averaged 21μ in thickness. The largest blastomere measured 97μ by 73μ , and the two smaller ones, 62μ by 62μ , and 50μ by 63μ , respectively.

The ovum was fixed, serially sectioned, and stained in the same manner as the second egg, described above. Since it includes ten sections, cut at 8μ , the specimen is approximately 80μ thick, again a shrinkage of about 50 per cent, attributable to fixation. A section through the middle of the egg measures 50μ by 86μ (Fig. 3B). The largest blastomere is here seen to measure 66μ by 49μ , and the two smaller ones, 35μ by 38μ , and 33μ by 44μ , respectively. Several round bodies are noted in the largest blastomere. These are shown more clearly in another section (Fig. 3C) in which they are seen to be present in each of the three blastomeres. They are probably nucleoli, similar to those observed in the corresponding stage of the mouse egg fertilized in vivo (cf. Lewis and Wright¹⁴—Plate 2, Fig. 15).

In a third section (Fig. 3D), there is a structure at "11 o'clock," measuring 14μ by 9μ , which is strongly suggestive of a polar body. Nowhere throughout the preparation is there any sign of the zona pellucida; this had evidently been dissolved by the fixative.

Comparison of Two- and Three-Cell Human Eggs With Similar Stages of Other Mammalian Eggs

In regard to the duration of early cleavage stages, it is pertinent to cite the report of Lewis and Hartman¹⁶ on the culture in vitro of the monkey egg fertilized in vivo. In their experiment, in which fertilization was believed to have occurred soon after ovulation, the minimum duration of the one- and two-cell stages was thought to be thirty-six and one-half hours. We observed two eggs in the two-cell stage forty and one-half and forty-five hours, respectively, following contact with spermatozoa. Since, in the monkey egg studied

Fig. 2.—No. 14,518. Human egg in two-cell stage: second specimen. This egg was washed out of an ovarian follicle of a 31-year-old white woman after laparotomy on the eleventh day of the cycle. After having been washed in Locke's solution, the egg was cultured in the patient's serum for twenty-two and one-half hours, was again washed in Locke's solution, and was exposed in vitro for two hours at room temperature to a washed suspension of human spermatozoa in Locke's solution. It was then washed in Locke's solution and incubated for forty-five hours at 37.5°C . in serum from a 62-year-old female patient.

A. Photograph of egg (after forty-five hours' incubation) showing two blastomeres within zona pellucida. At the margin of the latter are numerous spermatozoa, and at least one is seen within the zona. The entire egg (including the zona pellucida) measured 153μ by 155μ ; the vitellus was 100μ by 113μ , and the average thickness of the zona was 23μ . The blastomeres measured 88μ by 58μ , and 105μ by 58μ , respectively. ($\times 200$.) (Cf. Lewis and Hartman¹⁶—Plate 1, Fig. 7, and Lewis and Wright¹⁴—Plate 1, Fig. 10, for similar stages of monkey and mouse egg, respectively.)

B. Section through the middle of the egg. The egg, transferred to a plasma drop, was fixed with Bouin's solution, and the plasma drop was dried by warming it under a lamp. The resulting clot was carried through the double embedding celloidin-paraffin method, serially sectioned at 8μ , and stained with hematoxylin and eosin. Two blastomeres (one slightly larger than the other), containing granular cytoplasm, are enclosed within a zona pellucida which surrounds the egg over about two-thirds of its circumference. Failure to retain the entire zona in section is ascribed to the method of fixation. Several dark bodies suggestive of sperm heads may be identified; one of them appears to be just within the cell body of blastomere "B" (near "1 o'clock").

Since the egg is included in eight sections, its total thickness after fixation is ca. 64μ . This section, excluding the imperfect zona, measures 50μ by 75μ . The blastomeres, designated, for convenience, as "A" and "B," from left to right, measure 63μ by 39μ , and 66μ by 26μ , respectively. The nucleus in "A" measures 18μ by 13μ , and that in "B," 16μ by 15μ . In a well-defined portion (near "1 o'clock"), the zona measures 7μ to 8μ across. ($\times 600$.)

C. Another section of the same egg, adjacent to the one described above. This section, torn during cutting, is reproduced to show (besides blastomere "A") a polar body, measuring 18μ by 10μ , and containing chromatin units, two of which are clearly demarcated from the general mass. ($\times 500$.)

The Three-Cell Stage

The third experiment to be reported was performed on ova of a 38-year-old patient (No. 21,012), in whom the diagnosis of tuberculous endometritis had been made after routine biopsy taken in the course of an investigation for sterility. Operation, which consisted of complete hysterectomy, right oöphorectomy, and bilateral salpingectomy, was performed on the twelfth day of the cycle. The endometrium was found to be in the late proliferative stage. The two cycles immediately preceding operation had been thirty days long. Tissue examination showed the uterus and tubes to be extensively involved by the tuberculous process; both tubes were sealed and the fimbriae were inverted.

Four eggs, recovered in washings of incised follicles, were subjected to essentially the same procedures as outlined above. After such treatment, two of them were found in the three-cell stage.

These eggs were obtained from two medium-sized follicles in the right ovary, about four and one-half hours following oöphorectomy. After having been washed three times in Locke's solution, the ova were transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that had been obtained from the egg donor four hours previously. The preparation was then placed in the incubator at 37.5° C. At this time, the ova had been at room temperature for about five hours; i.e., the interval since oöphorectomy.

After twenty-seven hours of incubation, the eggs were washed three times in Locke's solution and were then exposed to a sperm suspension prepared from the same donor and in essentially the same manner as in the two experiments described above. At the time when the spermatozoa were added to the egg, the former had been at room temperature for four and one-half hours; i.e., the interval since ejaculation.

After having been in contact with the spermatozoa for one hour and ten minutes at room temperature, the ova, along with some of the surrounding sperm suspension, were transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that had been given about eight hours previously by a 53-year-old postmenopausal patient. The eggs were then incubated for forty-six hours at 37.5° C.

At the end of this period, since the ova could not be identified in the flask because of some contamination, the contained fluid was emptied into a watch glass, and sketches of the eggs were made under the high power of the compound microscope.

At this time, the more normal of the two specimens consisted of three round, regular blastomeres, two of nearly equal size, and one definitely larger. In each of them we observed a round, vesicular body which, at the time, we believed to be a nucleus. Within the next two hours, the egg, kept at room temperature, appeared distorted. At the moment, we regarded this as a degenerative phenomenon, but later we were reminded that Lewis and Hartman¹⁶ had noted such distortion in the dividing monkey egg during each of several early cleavages. A photograph of the egg (Fig. 3A), taken about two hours after it had been removed from the incubator, bears a striking resemblance both to the monkey egg (cf. Lewis and Hartman¹⁶—Plate 1, Fig. 9) and to the mouse egg (cf. Lewis and Wright¹⁴—Plate 2, Fig. 15) in a similar stage. In our human egg, as in the mouse and monkey eggs, the second cleavage plane is at right angles to the first one. The bulge at "5 o'clock" is believed to represent a polar body. The two pale round formations in the center of the egg may also be polar bodies (cf. Lewis and Wright¹⁴—Plate 2, Fig. 17). At least five dark objects assumed to be spermatozoa may be identified in the zona pellucida.

In a study of *in vivo* fertilized mouse eggs removed at different intervals after copulation, Lewis and Wright¹⁴ have found similar time relations to prevail: duration of one-cell stage, none to twenty-four hours; duration of two-cell stage, twenty-four to thirty-eight hours, and of three- and four-cell stage, thirty-eight to fifty hours. Hence, our findings in this respect are in general agreement with those reported for the mouse, as well as for the monkey egg. In evaluating these figures, one should of course bear in mind the probability, as pointed out by Lewis and Hartman,¹⁵ that the duration of cleavage stages is longer *in vitro* than *in vivo*.

In the rabbit, on the other hand, cleavage of the fertilized egg proceeds at a much faster rate.^{16, 22} Krassovskaja⁷ reported that the first cleavage of the rabbit egg began sixteen hours and forty minutes after spermatozoa had been added *in vitro*, and was completed forty-five minutes later; i.e., seventeen and one-half hours after insemination. The four-cell stage was attained twenty hours after the addition of spermatozoa to the egg. By the forty-sixth hour following *in vitro* insemination, Krassovskaja observed the 28-cell stage (morula). As has been noted above, our two human eggs, at a corresponding interval following insemination, had reached only the three-cell stage.

Fig. 3.—No. 21,012. Human egg in three-cell stage. This egg was washed out of an ovarian follicle of a 35-year-old sterility patient on the twelfth day of the cycle. After having been washed in Locke's solution, the egg was cultured in the patient's serum at 37.5° C. for twenty-seven hours, was again washed in Locke's solution, and was exposed *in vitro* for one hour and ten minutes at room temperature to a washed suspension of human spermatozoa in Locke's solution. It was then cultured for forty-six hours in serum from a 53-year-old postmenopausal patient.

A. Photograph of the egg (after forty-six hours of culture, followed by two hours at room temperature) shows it to have undergone definite changes since it was first seen in cleavage. Shrinkage and distortion in shape occurred in the interim, as well as vacuolization of the cytoplasm. Several dark bodies suggestive of spermatozoa are well defined within the zona pellucida.

The entire egg (including the zona pellucida) measured 170 μ by 153 μ . The vitellus was 103 μ by 127 μ , and the zona pellucida averaged 21 μ in thickness. The largest blastomere measured 97 μ by 73 μ , and the two smaller ones, 62 μ by 62 μ and 50 μ by 63 μ , respectively. The bulge at "5 o'clock" probably represents a polar body (cf. Lewis and Hartman¹⁵—Plate 1, Fig. 9, monkey egg). The two round pale objects in the center of the egg may also be polar bodies (cf. Lewis and Wright¹⁴—Plate 2, Fig. 17, mouse egg). (X300.)

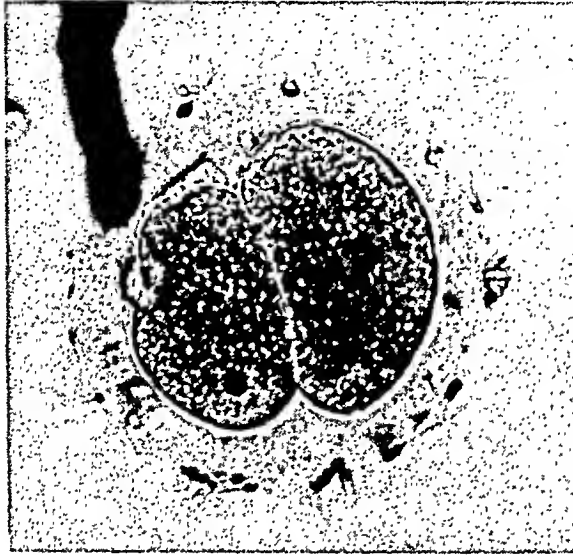
B. Section through the middle of the same egg. The egg, transferred to a plasma drop, was fixed with Bouin's solution, and the plasma drop was warmed. The resulting clot was carried through the double embedding celloidin-paraffin method, serially sectioned at 8 μ , and stained with hematoxylin and eosin. Three blastomeres are well defined, the two smaller ones being nearly equal in size. Note round bodies in the largest blastomere; these are probably nucleoli (cf. Lewis and Wright¹⁴—Plate 2, Fig. 15, mouse egg). The absence of the zona pellucida in the sections is doubtless due to the method of fixation, as it had been clearly seen in the fresh specimen.

Since there are ten sections, cut at 8 μ , the entire fixed egg is approximately 80 μ thick. This section measures 50 μ by 86 μ . The largest blastomere is here seen to be 66 μ by 49 μ , and the two smaller ones, 35 μ by 38 μ , and 33 μ by 44 μ , respectively. (X400.)

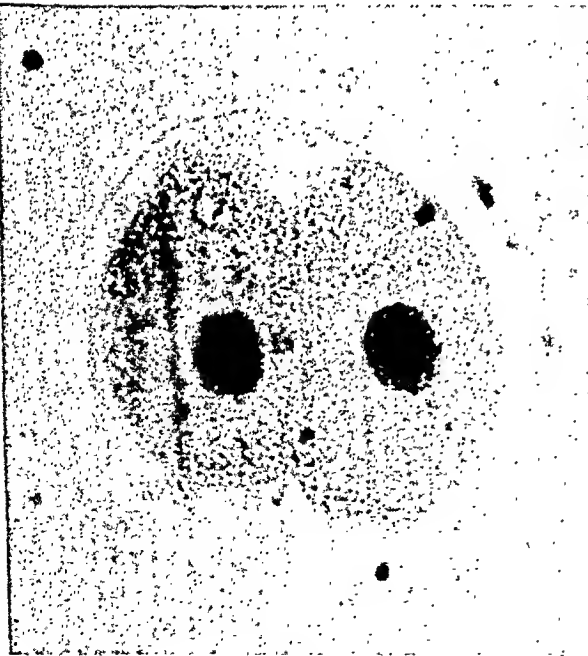
C. Another section of the same egg, showing the nucleoli more clearly. Here these appear in each of the three blastomeres. (X500.)

D. A third section of the same egg. Only two blastomeres are present in this section. An ovoid body, measuring 14 μ by 9 μ , and strongly suggestive of a polar body, is seen at "11 o'clock." (X500.)

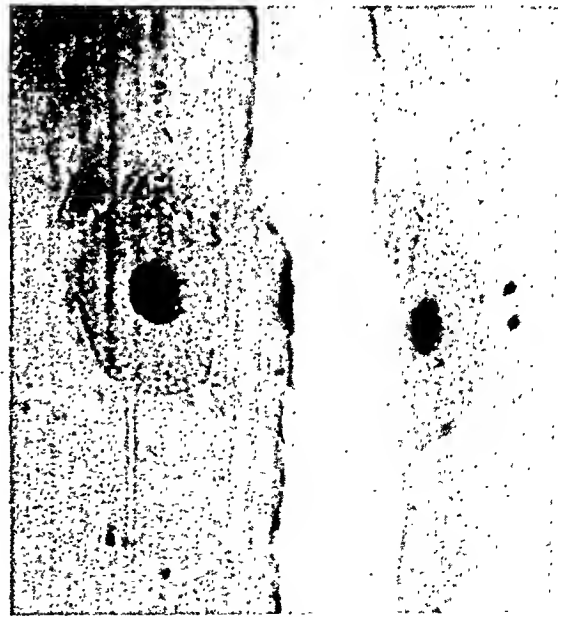
by Lewis and Hartman, the three-cell stage lasted less than one hour, the four-cell stage began at least thirty-seven and one-half hours, and ended at least forty-six and one-half hours following fertilization. Our two eggs were seen in the three-cell stage forty-six hours after exposure to spermatozoa. As Lewis and Hartman point out, a correction of two hours should be applied to their figures, since the egg was at room temperature for this period. On the other hand, since their values are "minimum" ones, the difference in the time relations between their results and ours cannot be regarded as a significant one.



A.



B.



C.

Fig. 2.—(See legend on opposite page).

In regard to the thickness of the zona pellucida, the average value for the mouse egg, in both the two-cell stage (36 eggs) and in the four-cell stage (fifteen eggs), as computed from figures listed by Lewis and Wright,¹⁴ is 11.5μ . Calculations made from data tabulated by Lewis and Hartman¹⁵ show the average thickness of the zona pellucida in tubal monkey eggs to be 11.2μ for the two-cell stage (three eggs), and 16.5μ for the four-cell stage (two eggs). The zona pellucida in our human eggs measured 14μ and 23μ , respectively, for the two eggs of the two-cell stage, and 21μ for the three-cell egg. Whether or not these figures have any significance cannot be ascertained until more human specimens are available.

Summary

Two human ovarian eggs were found to be in the two-cell stage, and two in the three-cell stage, after in vitro exposure to human sperm suspensions, preceded and followed by culture in human blood serum. The time relations in these experiments are in general accord with those reported previously for the in vivo fertilized tubal monkey egg cultured in vitro, as well as for in vivo fertilized mouse eggs studied at different intervals after copulation.

We very gratefully acknowledge the invaluable advice and encouragement generously given us by Doctor Gregory Pincus, as well as the helpful assistance furnished at various stages by Doctor Nicholas T. Werthessen, Miss Lotte Leo Siegel, Miss Eleanor C. Adams, Mr. James M. Snodgrass, Doctor Stephen Fleck, and Doctor Harold Brown. We are also deeply indebted to Doctor Austin M. Brues for his help in the early part of the investigation, and to Doctor Arthur T. Hertig for his constant encouragement, advice, and material aid through his grant from the Carnegie Corporation of New York. We are grateful also to Doctor Warren H. Lewis of the Wistar Institute of Anatomy and Biology for reviewing this report.

The sections of two of the eggs described in this paper are in the custody of the Department of Embryology, Carnegie Institution of Washington, Baltimore, Maryland. The two-cell egg is labeled Carnegie No. 8260, and the three-cell egg is Carnegie No. 8500.1.

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It is also of interest to compare the sizes of our human eggs with those of single mouse and monkey eggs in comparable stages, as illustrated in the respective monographs of Lewis and Wright¹⁴ and of Lewis and Hartman.¹⁶ The following figures were obtained by averaging the horizontal and vertical diameters of single and similar eggs (as represented in their respective photographs).*

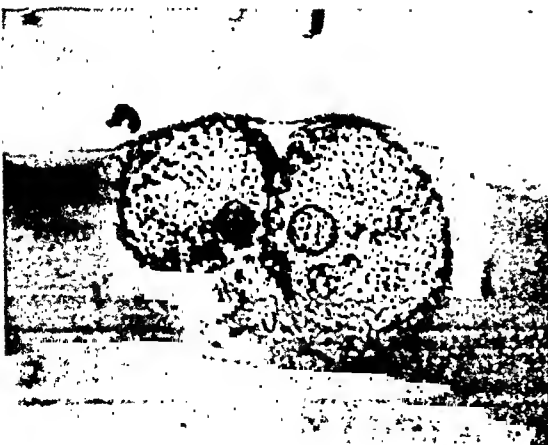
| | MOUSE | MONKEY | MAN |
|------------------|---|--|------------------------------------|
| Two-cell stage | 101 μ (Plate 2, Fig. 13) ¹⁴ | 153 μ (Plate 1, Fig. 7) ¹⁶ | 154 μ (Fig. 2A, This Paper) |
| Three-cell stage | 105 μ (Plate 2, Fig. 15) ¹⁴ | 145 μ (Plate 1, Fig. 9) ¹⁶ | 177 μ (Fig. 3A, This Paper) |



A.



B.



C.



D.

Fig. 3.—(See legend on opposite page.)

*In evaluating these figures, it should be noted that appreciable variation in the size of eggs of a particular stage has been reported in several species.

Procedure and Methods

During the course of this study, vaginal smears for cytologic examination were taken on all patients admitted to the gynecologic wards, usually within forty-eight hours of their admission, care being exercised not to take smears within twenty-four hours of a vaginal douche or other procedures which might interfere with the collection of the material or staining reaction. The smears were taken by a single technician who had several years of training in this work; if any difficulties were encountered she was assisted by the resident on the service. The technique employed was essentially that described by Papanicolaou and Traut. A slightly curved glass pipette attached to a strong rubber bulb was introduced into the posterior fornix of the vagina. As aspiration was in progress the tip of the pipette was rotated into all portions of the posterior vagina in order to obtain a representative sample. When the pipette was withdrawn the secretion was blown onto the surface of two clean glass slips. The material was then further spread with the convex side of the pipette and immediately dropped into a Coplin jar containing equal parts of 95 per cent alcohol and ether, special care being taken to prevent drying before fixation. The smears were taken to the laboratory and the preparation of the slides was completed promptly, employing the techniques described by Papanicolaou. One slide was prepared with stain EA 31, and the other with stain EA 36,* since somewhat different staining reactions often afford additional information. Each slide was read at least twice, and all abnormal or unusual cells were marked with a finder for further review, if necessary. For purposes of this study it was decided to classify each slide as positive or negative and to omit the designation of doubtful for statistical evaluation. This decision was reached because in many instances it would not have been possible to obtain repeat smears because of intervening surgical procedures.

The criteria by which a slide was considered as suggestive of malignancy corresponded in general to those outlined by Papanicolaou and Traut. Emphasis was placed on abnormalities in size, morphology, and staining reaction of the nuclei. Bizarre morphology and size of the cell, abnormalities in the staining reaction, and character of the cytoplasm were considered suspicious and warranted more intensive search for abnormal cells, but a diagnosis of malignancy was not made on the latter criteria alone. The presence of red cells, histiocytes, giant cells, and increased numbers of leucocytes were almost always found in positive smears, so that their mere presence was regarded with suspicion, but these same cells may be found in benign conditions, particularly those eliciting an inflammatory response.

Each slide was marked by a number and was so reported, so that the patient and the clinical history were entirely unknown to the reader of the slides. On the other hand, the pathologic diagnosis of removed tissue was submitted by the pathologist (Dr. J. Hoffman) without any knowledge on his part of the findings of the cytologist (Dr. A. E. Rakoff). In instances where no gynecologic operative procedure was carried out, the diagnosis was established clinically. The study was continued until 500 consecutive cases had been completed.

Results

Among the 500 consecutive gynecologic patients in this study, sixty-three patients had cancer of the uterus proved by histologic examination of tissue removed by biopsy or at operation (Table I). There were fifty-seven

*These stains were generously furnished through the courtesy of the Ortho Research Foundation, Raritan, New Jersey. At present we are also using stain EA 50, which gives excellent cytologic detail.

AN EVALUATION OF THE VAGINAL SMEAR METHOD FOR THE DIAGNOSIS OF UTERINE CANCER*

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ALMOST two decades have elapsed since Papanicolaou¹ first pointed out that exfoliated cancer cells shed from a uterine malignant growth could be found and recognized in smears prepared from the vaginal secretion. It has been only in the last five years, however, that this observation has received widespread attention as a diagnostic procedure for the detection of uterine cancer. In 1943 Papanicolaou and Traut² published their monograph on the "Diagnosis of Uterine Cancer by the Vaginal Smear" based on the examination of smears from 3,014 women, of whom 179 were found to have cancer which was primary in the uterus. Much interest was aroused by this work because of the high degree of accuracy which was claimed for the method as well as the excellent descriptions and colored plates of the various cells which could be found in the vagina in normal patients, in those with various functional abnormalities, and in patients with uterine carcinoma. It was apparent from their studies that the successful application of this method necessitated considerable experience, since the cytologic changes in the cells which one might encounter in such smears are most variable. It is not remarkable therefore, that although interest in the subject has been keen, the general application of this method necessarily has been slow. The several reports which have since appeared, particularly those by Meigs and his associates;³ Fremont-Smith and associates;^{4, 5} Jones, Neustadter, and Mackenzie;⁶ as well as Ayre,⁷ have been quite enthusiastic and have encouraged others to make use of this diagnostic aid. Our own experience with this technique is now of four years' standing, and covers approximately five thousand cases, which include patients in the gynecologic wards and clinics of the Jefferson Hospital, patients from the private practices of our staff, and from women attending various Health Maintenance and Cancer Prevention-Detections clinics throughout the city of Philadelphia. During the course of our work, the advisability of running a carefully controlled study on all patients admitted to the gynecologic wards became apparent. The purpose of this study was to determine the value of the vaginal smear as a routine procedure for the diagnosis of uterine cancer in gynecologic patients admitted to the ward.

*Aided by a grant from the Ortho Research Foundation, Raritan, New Jersey.
Read before The Philadelphia Obstetrical Society, May 1, 1947.

Review of the slides in which the diagnosis of squamous cell carcinoma had been missed showed the presence of normal cervical cells in all cases. In most of the slides in this group, the cervical cells were present in increased number, and in a high percentage there were also many red cells, histiocytes and an increased number of leucocytes. In three of the cases cervical cells were seen which were considered bizarre but not thought to be of the malignant type. These smears would ordinarily have been classified as doubtful and would have been repeated but for the specific nature of this study. In the remaining 14 cases, however, no real suspicion of malignancy was excited.

The two cases of fundal carcinoma which were missed cytologically showed increased numbers of endometrial cells with evidence of bleeding and inflammation as well. However, the cells did not present more than a normal variation in size, nor did the nuclei exhibit abnormal morphology or unusual hyperchromatic staining.

The final diagnoses based on pathologic and/or clinical findings in patients in whom the smears were incorrectly classified as positive are given in Table V.

Discussion

It is the opinion of those who have worked most with the vaginal cytology smear for the diagnosis of uterine cancer that this procedure has real merit. However the most enthusiastic workers in this field acknowledge that there are definite limitations in its application and usefulness. The warning has been stressed repeatedly that the vaginal cytology smear is not intended to replace biopsy of the cervix or diagnostic curettage of the fundus as the sole criterion for diagnosis and treatment. Even in the most competent hands it is freely acknowledged that some cases of carcinoma will be missed by the vaginal smear method and on occasion an apparent diagnosis of carcinoma will be suggested by the vaginal smear in patients subsequently proved to have nonmalignant lesions. The statistical accuracy of the procedure has been reported upon by several groups of workers. Papanicolaou and Traut² failed to detect malignant cells in the vaginal smears of patients with demonstrable carcinoma of the cervix in only four of 127 patients, and failed to diagnose carcinoma of the fundus in seven of fifty-three patients with this condition, thus giving an incidence of false negative smears for the cervical cases of 3.2 per cent, and for the fundal cases of 9.3 per cent. In 1945 Meigs³ reported a series of 1,015 cases with an over-all error of 4 per cent. In a more recent review of 1,875 cases studied in the laboratory of the Vincent Memorial (Massachusetts General) Hospital, Fremont-Smith and Graham⁵ found the procedure to have an over-all diagnostic accuracy of over 96 per cent. However, further scrutiny of their statistics shows that the percentage error in patients with proved carcinoma is considerably higher than in the negative cases. Thus, an incorrect negative diagnosis was made in 10.3 per cent of 154 carcinoma cases, while false positives were reported in 2.9 per cent of 861 negative cases, although the over-all total diagnostic error was but 4 per cent. It is apparent that the latter figure was much influenced by the high proportion of negative cases. Ayre,⁷ in a study of 580 cases, reported missed diagnoses amounting to 6 per cent in 100 patients who had a positive tissue diagnosis of malignancy. False positive smears however, occurred in only nine patients, or 1.9 per cent of the 475 who were negative for carcinoma.

patients with squamous-cell carcinoma of the cervix, five patients with adenocarcinoma of the endometrium, and one patient with a fibrosarcoma of the uterine fundus. Of the 437 patients who were classified as negative for uterine cancer, approximately two-thirds had various operative procedures which provided tissue for histologic examination. The remaining patients had various gynecologic or related conditions in which operation was not necessary for diagnosis or treatment.

TABLE I. FINAL DIAGNOSIS IN PATIENTS STUDIED

| | | |
|------------------------------|-------------|-------------|
| Total No. of Patients | | 500 |
| Patients with Uterine Cancer | | 63 or 12.6% |
| Cervical: Squamous cell | 57 or 90.5% | |
| Adenocarcinoma | 0 | |
| Fundal: Adenocarcinoma | 5 or 7.8% | |
| Fibrosarcoma | 1 or 1.8% | |

The findings of the vaginal cytology smears with respect to cells suggesting uterine cancer are summarized in Table II. For the entire group the smear gave a correct correlation in 94.8 per cent of the cases. It will be noted at once, however, that correct results were far better for the large group of patients who did not have cancer than for the smaller group who did have a uterine malignancy (Tables III and IV). False positives occurred in seven, or only 1.6 per cent of the 437 negative patients, while the diagnosis was missed in nineteen, or 30 per cent of the sixty-three positive cases.

TABLE II. RESULTS OF SMEARS FOR ENTIRE GROUP (500 PATIENTS)

| | NO. | | PER CENT |
|-------------------|-----|----|----------|
| Correct results | 474 | or | 94.8 |
| Correct positive | 44 | | |
| Correct negative | 430 | | |
| Incorrect results | 26 | or | 5.2 |
| False positive | 7 | | |
| False negative | 19 | | |

TABLE III. RESULTS OF SMEARS IN CANCER PATIENTS

| NO. OF PATIENTS | ENTIRE GROUP | CERVICAL CANCER | FUNDAL CANCER* |
|-------------------------|--------------|-----------------|----------------|
| | 63 | 57 | 6 |
| Correct positive smears | 44 or 70.0% | 40 or 70.2% | 4 or 66.7% |
| False negative smears | 19 or 30.0% | 17 or 28.8 % | 2 or 33.3 % |

*Including one case of fibrosarcoma, diagnosed on smears as "malignant, probably cervical."

TABLE IV. RESULTS OF SMEARS IN NEGATIVE PATIENTS

| | |
|-------------------------|--------------|
| No. of patients | 437 |
| Correct negative smears | 430 or 98.4% |
| False positive smears | 7 or 1.6% |

There were but five patients with fundal carcinoma. In two of the cases the vaginal smear was reported as negative. There was one case of fibrosarcoma of the uterus, which was correctly reported as positive for uterine malignancy; however in this instance, the type of malignancy was questionable on the basis of the smear, and was finally incorrectly reported as cervical in origin. The abnormal cells noted on the smear were of the elongated spindle variety. The fifty-seven cases of cervical carcinoma were all of the squamous type. A diagnosis of squamous cell carcinoma of the cervix was made by the vaginal smear in forty, or 70.2 per cent of the cases, and missed in seventeen, or 28.8 per cent.

has been our policy, since the completion of this study, that whenever large numbers of cervical or endometrial cells are found which are at all bizarre to ask for repeated smears. Not infrequently much repetition has been rewarded by eventually finding cells suggestive of malignancy. On the other hand, it has been pointed out in the results presented that there have been numerous instances in which the initial smear failed to arouse sufficient suspicion to warrant further investigation. This we regard as the chief danger of the vaginal cytologic method, namely, the false security that a negative report may engender, particularly among those who do not appreciate its limitations.

(3) *The Personal Factor.*—There can be no question that the successful use of the vaginal smear method, even in the hands of competent microscopists, depends largely upon a wide experience in interpreting the cells which may be found on the smears. A large variety of cells which normally may be found in the vagina arise from all parts of the genital tract, and variations due to age, alterations in ovarian activity, functional disturbances, inflammatory reactions, and various benign growths, make it most difficult to evaluate cells regarded as suspicious of malignancy. In analyzing the statistics from different clinics it is quite apparent that the personal factor has been an important one, since some groups have a considerable error in false positives while in others the percentage of false negatives has been greater. Our own practice has been to adopt a rather rigid standard in reporting smears suspicious of malignancy and to indicate other smears containing cells not fully meeting these requirements as "doubtful." Much can be said on both sides of this question. If the diagnostic criteria are made too rigid it is quite possible that positive cases will be overlooked. On the other hand, if smears are reported positive on an insecure basis, unnecessary biopsies or even operations may be performed. Even with our most rigid standards we have had several instances in which biopsy or operation failed to reveal a malignant lesion; yet these have been more than compensated for with several cases in which operation was performed on the basis of a vaginal smear alone and in which carcinoma was found. One such case proved to be a myosarcoma of the tube and in another instance an endometrial carcinoma was discovered in patients not included in this study.

A point not to be overlooked in a study of this kind is the value of the vaginal smear in furnishing information concerning the patient other than the presence of malignant cells. The usefulness of the cytologic smear of determining ovarian function is now well established. Although the cytologic findings in pregnancy are not absolutely characteristic the experienced observer soon learns to detect cells suggesting this possibility in a fairly high percentage of the cases. If in addition one finds evidences of bleeding, plus the presence of decidual cells or even cells from the trophoblast, the diagnosis of threatened abortion is frequently suggested. The vaginal smear picture in cervical infections is also often quite characteristic, being evidenced by large numbers of cells from the exocervix and from the endocervix, much mucus and large numbers of leucocytes. Trichomonads and fungi can quite readily be detected on these smears, even though the stains used are not ideal for their demonstration. Pelvic inflammatory disease often presents a vaginal smear most difficult of evaluation and in some instances the cells present are not only bizarre but sometimes suggestive of malignancy. In the present study as well as in our general experience, pelvic inflammatory disease is more likely to be responsible for a false positive smear than any other type of lesion. Cervical polyps present a problem also in that large numbers of cervical cells are present, often of bizarre shape, but usually with fairly normal looking nuclei. These are but a few of the problem pictures which the vaginal cytology smear may present.

Jones and her co-workers⁶ had an error of 11 per cent in false positives and 9 per cent in false negatives in a group of 432 cases, in eighty-two of which a final diagnosis of malignancy was established.

TABLE V. PATIENTS WITH FALSE POSITIVE SMEARS

| FINAL DIAGNOSIS | VAGINAL SMEAR |
|--------------------------------|-------------------------|
| Age 52 years | |
| 1. Hyperplastic endometrium | Squamous cell carcinoma |
| Fibromyomata | |
| Age 44 years | |
| 2. Functional uterine bleeding | Endometrial carcinoma |
| Age 22 years | |
| 3. Pelvic inflammatory disease | Squamous cell carcinoma |
| Age 28 years | |
| 4. Pelvic inflammatory disease | Squamous cell carcinoma |
| Age 18 years | |
| 5. Pelvic inflammatory disease | Squamous cell carcinoma |
| Age 24 years | |
| 6. Abortion induced? | Endometrial carcinoma |
| Age 55 years | |
| 7. Cervical polyp benign | Squamous cell carcinoma |

It will be note that these statistics, including those reported in the present study, show a considerable degree of variation. This may be attributed to a number of faetors inherent in the technique, which may be most conveniently summarized under the following headings:

(1) *Collection of Vaginal Smears.*—There has been considerable diseussion as to whether smears should be collected from the posterior fornix of the vagina as originally advocated by Papanicolaou or from the cervix as advocated by Ayre and his associates.⁸ Endocervical and endometrial smears also were suggested by Papanicolaou⁹ as a further diagnostic aid in selected cases. It has been pointed out that the posterior fornix is the natural collecting place for exfoliated cells from every portion of the genital tract and that material collected from this source is most likely to be representative of all portions. On the other hand, if a lesion is visible or accessible, material collected from such a source is most likely to contain a higher proportion of abnormal cells. The perecentage of endometrial cells has been claimed to be higher in the cervical secretion than in the vaginal smear. Although the present study was limited to smears taken only from the vagina, other observations which we have made lead us to believe that for routine purposes smears taken from both sources are probably better. We have noted occasional instances in which vaginal smears failed to show abnormal cells although the latter were found in smears prepared from the cervix. Nevertheless, cervical smears alone have not proved generally to be more accurate, in our experience, than those from the vaginal source alone. It has been our recent practice, therefore, to collect both cervieal and vaginal smears wherever possible.

(2) *The Number of Smears Examined.*—Unquestionably the larger the number of samplings taken from a patient, the more accurate the results. This factor is an important one and probably explains the remarkable statistics reported by Papanicolaou and Traut,² since they state that many smears were taken from the patients they studied. Unfortunately, this has a certain practical limitation, since if the smear is completely negative and the patient presents no suspicious symptoms or lesions, there would be little reason for repeating smears. It was with this thought in mind that the present study was limited to a single set of smears, and it is our opinion that the high percentage of positive cases missed can be attributed chiefly to this factor. It

6. The value of the vaginal smear as a routine procedure on the gynecologic service is indicated as a diagnostic aid not only in the detection of uterine cancer but in affording information concerning the functional status of the patient and infections of the genital tract.

7. The necessity for recognizing the limitations of the cytologic method is emphasized since its indiscriminate use may lead to failure of employing more absolute methods of diagnosis or indiscriminate surgery.

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In conclusion, the present study corroborates the general value of the vaginal smear technique as a useful procedure for the routine study of gynecologic patients, and for the routine study prescribed in Health Maintenance and Cancer Prevention-Detection Clinics. In other words, it offers a measure of further investigation in those patients presenting no abnormal symptomatology and no visible or palpable evidence of a lesion suspicious of malignancy. In this respect, if carefully and cautiously used, the vaginal smear technique may well take its place as a routine public health diagnostic measure. The results emphasize however, that reliance cannot be placed on a single set of smears for the detection of uterine malignancy, since a high percentage of cases will be missed. It emphasizes the importance of fully investigating every case which presents cells suggestive of malignancy, since the percentage of false positives is not high. If intelligently used as an adjunct to other well-recognized procedures, particularly biopsy and curettage, the vaginal smear may be employed with benefit not only for the detection of cancer but in obtaining useful information concerning the functional state of the ovaries, the presence of inflammatory lesions and benign tumors of the genital tract. If employed overenthusiastically without regard to its limitations, and the use of the vaginal smear technique may lead to failure to employ more absolute methods of diagnosis or indiscriminate surgery.

Summary

1. Vaginal smears for cytologic study were collected on 500 consecutive patients admitted to the gynecologic ward. The vaginal smears were read by number and later compared with the pathologic and clinical findings.

2. Sixty-three patients had proved uterine carcinomas, fifty-seven being squamous-cell carcinomas of the cervix, five were adenocarcinomas of the endometrium and there was one fibrosarcoma. The vaginal findings afforded correct correlation in 474, or 94.8 per cent of the 500 patients, forty-four being correct positives and 430 correct negatives. Incorrect results were obtained in twenty-six or 5.2 per cent of the cases, seven being false positives, and nineteen being false negatives.

3. In the sixty-three cancer patients, correct positive smears were obtained in forty-four, or 70.0 per cent. Negative smears were obtained in nineteen, or 30.0 per cent. In the fifty-seven cases of cervical cancer seventeen, or 28.8 per cent, were missed, while in the six patients with fundal cancer two, or 33.3 per cent, were not detected.

4. Excellent correlation was obtained in the 437 patients who did not have carcinomas; correct negative smears were obtained in 430, or 98.4 per cent, while false positives occurred in only seven, or 1.6 per cent. It is emphasized that the good over-all correlation of 94.8 per cent was largely influenced by the high proportion of negative patients and it is pointed out that this factor has influenced the results in some of the earlier studies by other workers.

5. The factors influencing the accuracy of the cytologic method for the diagnosis of uterine cancer are discussed. It is contended that smears taken from the vagina and the cervix are preferable to those from either source alone. The advantages of repeated samplings are emphasized by the high percentage of missed positive cases on a single sampling. The influence of the personal factor in the interpretation of atypical slides is pointed out.

TABLE I. (100,000 UNITS PENICILLIN)

| NAME | AGE | MENSTRUAL HISTORY | VAGINAL EXAMINATION | VAGINAL SECRETIONS | VAGINAL CULTURE | BLOOD LEVELS | | | | DATE |
|-------|-----|-----------------------------|--|---|--|--------------|-------|-------|-------|---------|
| | | | | | | 1/2 HR. | 1 HR. | 2 HR. | 3 HR. | |
| A. K. | 56 | Postmenopausal LMP 1939 | Senile vaginal mucosa with vaginitis | Not reported | Not reported | 1.0 | 1.0 | .50 | .25 | 7/5/46 |
| M. D. | 48 | Postmenopausal LMP 1930 | Senile vaginal mucosa with vaginitis | Few WBC Few bacteria | Diphtheroids; <i>B. Coli</i> | 1.0 | .50 | 0.0 | 0.0 | 8/23/46 |
| E. M. | 41 | LMP March, 1944 | Recent vaginal plastic operation; marked vaginitis | Many WBC Rare RBC Many bacteria | <i>Staph. albus</i> , non-hemolytic Alpha hemolytic streptococcus | 0 | 0 | 0 | 0 | 7/15/46 |
| R. K. | 30 | Cycle 28/5 LMP 7/10/46 | Endocervicitis; vaginitis with much leucorrhea | Moderate WBC Moderate bacteria Occ. RBC | Nonhemolytic <i>Staph. albus</i> | .125 | .125 | .06 | .03 | 7/15/46 |
| E. L. | 59 | Postmenopausal LMP 1937 | Senile vaginal mucosa with severe vaginitis and profuse leucorrhea | Many bacteria Many WBC | Nonhemolytic streptococcus | 0.0 | .06 | .05 | .06 | 7/10/46 |
| M. K. | 26 | Cycle 28/4 LMP 6/28/46 | Marked vaginitis | Many WBC Mod. bacteria Occ. tricho. | Nonhemolytic <i>Staph. albus</i> Hemolytic <i>Staph. albus</i> Nonhemolytic streptococcus | .03 | .03 | 0 | 0 | 7/15/46 |
| V. P. | 28 | Cycle 28-32/5 LMP 6/5/46 | Endocervicitis; vaginitis with much leucorrhea | Many WBC Many bacteria | Diphtheroids | .12 | .50 | .50 | .50 | 8/12/46 |
| M. D. | 25 | Cycle 28/5 LMP 7/7/46 | Severe vaginitis | Many WBC Many bacteria | Diphtheroids | .125 | 1.0 | .25 | .03 | 7/22/46 |
| E. L. | 53 | Postmenopausal LMP 1941 | Senile vaginal mucosa with vaginitis | Many WBC Many RBC Many bacteria | Nonhemolytic <i>Staph. albus</i> ; <i>B. Coli</i> | 4.0 | 1.0 | .25 | .06 | 7/3/46 |
| A. T. | 23 | Cycle 28/6 LMP 9/19/46 | Marked vaginitis with leucorrhea; typical trichomonas | Many WBC Many bacteria Many tricho. | Moderate gamma streptococcus and diphtheroids | .25 | .50 | .125 | .06 | 7/15/46 |

OBSERVATIONS ON VAGINAL ABSORPTION OF PENICILLIN*

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DURING a recent investigation of the value of penicillin vaginal suppositories in the treatment of vaginitis, concomitant observations were made relative to blood penicillin levels in the patients treated. Some interesting, if somewhat variable levels were obtained indicating inconsistent vaginal absorption in this group of patients with vaginitis. It seemed propitious to further our knowledge of the rate and degree of absorption of penicillin calcium from the vagina in a control group. Such a control group was organized from among our young single hospital nurses. Subjects in whom blood level studies were conducted were divided into four small groups as follows:

Group I is composed of ten patients from among the cases treated for vaginitis. The accompanying tables include the essential relevant data. One suppository containing 100,000 units of penicillin was inserted vaginally prior to the blood level studies in each patient.

Group II includes five additional patients with vaginitis in whom studies were made subsequent to the insertion of two suppositories (200,000 units). Table II follows.

Group III represents five hospital clinic patients selected at random for similar penicillin blood level studies following vaginal insertion of 200,000 units of penicillin. These five subjects were free of vaginal pathology. The pertinent detail in each case is included in Table III.

And finally, group IV is composed of nineteen of our single hospital nurses. These girls were contacted individually and told in detail of the proposed study. All were normal young menstruating women free of gynecologic pathology. Four studies were made in each volunteer at different stages during a menstrual cycle beginning at the completion of a period and ending just prior to the onset of the subsequent period. The blood levels in each instance again were determined following the vaginal insertion of two penicillin suppositories (200,000 units). During the ensuing four hours while the study was in progress, the girls were instructed to remain quietly in bed. Again the accompanying table includes the pertinent data.

The average blood levels for groups I, II and III are represented in the following graph. As seen in Table IV, the few levels obtained in group IV were so low as to be unassayable by the method used. Graphic representation of the results in group IV is not possible.

*Vaginal suppositories were generously supplied by the Schenley Corporation, New York.

TABLE III. (200,000 UNITS PENICILLIN)

| NAME | AGE | MENSTRUAL HISTORY | GYNECOLOGIC PATHOLOGY | BLOOD LEVELS | | | |
|-------|-----|--|---|--------------|-------|-------|-------|
| | | | | ½ HR. | 1 HR. | 2 HR. | 3 HR. |
| B. V. | 39 | LMP just prior to test—periods irregular | Had vaginal plastic No pathology now Vagina clean (intermenstrual spotting) | 0.0 | 0.0 | 0.0 | 0.0 |
| S. R. | 46 | Cycle 21-28/10 LMP 11/9 Test 11/19 | No pathology (menorrhagia) Vagina clean | 0.0 | 0.0 | 0.0 | 0.0 |
| N. D. | 51 | LMP 23 years ago following abdominal section | Large cysto- and rectocele Cervix and part of corpus seemed present (no vaginal pathology) | 1.0 | 2.0 | 1.0 | 0.50 |
| M. R. | 60 | LMP 19 years ago | No gynecologic pathology Vagina clean (Vaginal spotting?) | 0.0 | 0.50 | 0.50 | 0.50 |
| H. L. | 43 | Cycle 28/5 LMP 3 weeks prior to test | Cystocele and rectocele Vagina clean | 0.0 | 0.25 | 1.0 | 0.25 |

The method of assay employed for this work was the Fleming-Wright slide cell technique as described by Heilman and Herrill¹ with the omission of dilution transfer to the slides. Defibrinated rabbit blood containing a beta hemolytic streptococcus sensitive to penicillin (culture (203) was added to the serial dilutions of the serums and incubated overnight. On the following day the assay was observed for presence or absence of hemolysis. The last tube of the serial dilution containing blood serum showing no hemolysis was taken as the end point and its contents of penicillin was considered identical to that of a standard prepared similarly containing a known amount of penicillin.

Discussion

From the results obtained one is impressed with the extreme variability of blood penicillin levels following insertion of penicillin vaginal suppositories. It is interesting to note the marked differences in levels obtained among individual patients within the same group. The lack of appreciable levels in the well-controlled group of nurses is particularly striking. A short comment relative to the few recent articles dealing with vaginal absorption of penicillin seems appropriate before attempting to evaluate our own results.

Lovelady, Randall, and Hosfeld² reported blood penicillin levels in thirty-six postpartum patients following the insertion of vaginal suppositories. These patients were confined to bed. No mention is made of the elapsed time since the patients were delivered. The thirty-six patients were divided into three groups of one dozen each. In the first group one suppository was used (100,000 units penicillin), in the second group two suppositories were used, and in the third group three suppositories were used. Levels were determined at three and five hours by the slide-cell technique of Heilman. In group one, five patients showed a low blood level after three hours and seven did not. There were no levels at five hours. Six of the patients in group II showed a somewhat higher level at three hours and in two of these there was still an appreciable level at five hours. In group III all but three of the twelve patients showed levels at three hours,

TABLE II. (200,000 UNITS PENICILLIN)

| NAME | AGE | MENSTRUAL HISTORY | VAGINAL EXAMINATION | VAGINAL SECRETIONS | VAGINAL CULTURE | BLOOD LEVELS | | | | DATE |
|-------|-----|---|--|---|--|--------------|-------|-------|-------|----------|
| | | | | | | 1/2 HR. | 1 HR. | 2 HR. | 3 HR. | |
| C. W. | 34 | Cycle 28/5 LMP 7/22/46 | Severe vaginitis; typical tricho. | Many WBC Many bacteria Many tricho. | Diphtheroids Micrococcus Alpha streptococcus | 0.0 | 0.0 | .125 | 0.0 | 7/30/46 |
| C. B. | 59 | Postmenopausal LMP 1941 | Senile vaginal mucosa with vaginitis | Many WBC Many bacteria | Diphtheroids Alpha streptococcus | 0.0 | 0.0 | 0.0 | 0.0 | 7/30/47 |
| J. F. | 23 | Cycle 21/3 LMP 6/8/46 | Endocervicitis and vaginitis | Many WBC Many bacteria | Diphtheroids Staph. albus | 0.0 | .25 | 1.0 | 2.0 | 10/23/47 |
| E. L. | 59 | Postmenopausal LMP 1937 | Senile vaginal mucosa with vaginitis and severe leucorrhea | Many WBC Many bacteria | Nonhemolytic streptococcus | 2.0 | 1.0 | .125 | 0.0 | 11/15/46 |
| L. C. | 31 | Abd. complete hysterectomy in April, 1946; both ovaries left in | Vaginitis | Many WBC Many bacteria | Alpha streptococcus B. Subtilis | 0.0 | .25 | .25 | .25 | 8/13/46 |

TABLE IV. (200,000 UNITS PENICILLIN)

| NAME | AGE | MENSTRUAL HISTORY | DAY OF CYCLE | BLOOD LEVELS | | | |
|-------|-----|------------------------------|-----------------|--------------|-------|-------|-------|
| | | | | 1 HR. | 1 HR. | 2 HR. | 3 HR. |
| A. A. | 22 | Cycle 28/7 LMP 1/1/47 | 1/ 6/47 | 0 | 0 | 0 | 0 |
| | | | 1/13/47 | 0 | 0 | 0 | 0 |
| | | | 1/20/47 | 0 | 0 | 0 | 0 |
| | | | 1/23/47 | 0 | 0 | 0 | IC |
| A. H. | 26 | Cycle 28-30/4 LMP 1/2/47 | 1/ 6/47 | 0 | 0 | 0 | 0 |
| | | | 1/14/47 | 0 | 0 | 0 | 0 |
| | | | 1/21/47 | 0 | 0 | 0 | 0 |
| | | | 1/29/47 | 0 | 0 | 0 | 0 |
| M. K. | 26 | Cycle 30/7-8 LMP 12/29/46 | 1/ 6/47 | 0 | 0 | 0 | 0 |
| | | | 1/13/47 | 0 | 0 | 0 | 0 |
| | | | 1/20/47 | 0 | 0 | 0 | 0 |
| | | | 1/27/47 | 0 | 0 | 0 | 0 |
| D. O. | 24 | Cycle 28/4 LMP 1/3/47 | 1/ 7/47 | 0 | 0 | 0 | 0 |
| | | | 1/15/47 | 0 | 0 | 0 | 0 |
| | | | 1/23/47 | IC | 0 | 0 | 0 |
| C. U. | 25 | Cycle 21/5 LMP 1/5/47 | 1/ 9/47 | 0 | 0 | 0 | 0 |
| | | | 1/14/47 | 0 | 0 | 0 | 0 |
| | | | 1/21/47 | 0 | 0 | IC | 0 |
| | | | 1/25/47 | 0 | 0 | 0 | 0 |
| S. H. | 27 | Cycle 22/7 LMP 1/7/47 | 1/13/47 | 0 | 0 | 0 | 0 |
| | | | 1/20/47 | 0 | 0 | 0 | 0 |
| | | | 1/27/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 2/47 | 0 | 0 | 0 | 0 |
| W. F. | 24 | Cycle 30/5 LMP 1/7/47 | 1/11/47 | 0 | 0 | 0 | 0 |
| | | | 1/20/47 | 0 | 0 | 0 | 0 |
| | | | 1/28/47 | IC | IC | 0 | 0 |
| | | | 2/ 6/47 | 0 | 0 | 0 | 0 |
| A. G. | 26 | Cycle 28/4 LMP 1/29/47 | 2/ 3/47 | 0 | 0 | 0 | 0 |
| | | | 2/10/47 | 0 | 0 | 0 | 0 |
| | | | 2/17/47 | 0 | 0 | 0 | 0 |
| | | | 2/24/47 | 0 | 0 | 0 | 0 |
| A. H. | 25 | Cycle 30/5 LMP 1/5/47 | 1/ 9/47 | 0 | 0 | 0 | 0 |
| | | | 1/17/47 | 0 | 0 | 0 | 0 |
| | | | 1/27/47 | 0 | 0 | IC | 0 |
| | | | 2/ 3/47 | 0 | 0 | 0 | 0 |
| R. W. | 23 | Cycle 28/5 LMP 1/13/47 | 1/18/47 | 0 | 0 | 0 | 0 |
| | | | 1/27/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 2/47 | 0 | 0 | 0 | IC |
| | | | 2/ 8/47 | 0 | 0 | 0 | 0 |
| C. C. | 22 | Cycle 28/5 LMP 1/12/47 | 1/18/47 | 0 | 0 | 0 | 0 |
| | | | 1/25/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 1/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 8/47 | 0 | IC | IC | 0 |
| J. B. | 25 | Cycle 28/4-5 LMP 1/15/47 | 1/20/47 | 0 | 0 | 0 | 0 |
| | | | 1/28/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 5/47 | 0 | 0 | 0 | 0 |
| | | | 2/13/47 | 0 | 0 | 0 | 0 |
| C. C. | 23 | Cycle 25/5 LMP 1/10/47 | 1/14/47 | 0 | 0 | 0 | 0 |
| | | | 1/21/47 | 0 | 0 | 0 | 0 |
| | | | 1/28/47 | 0 | IC | 0 | 0 |
| | | | 2/ 4/47 | 0 | 0 | 0 | 0 |
| E. A. | 26 | Cycle 28/4-5 LMP 1/9/47 | 1/14/47 | 0 | 0 | 0 | 0 |
| | | | 1/21/47 | 0 | 0 | 0 | 0 |
| | | | 1/28/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 6/47 | 0 | 0 | 0 | 0 |

one as high as 0.5 units per c.c. serum. Appreciable levels were maintained in seven of these patients for 5 hours. From their results the Mayo group advocated the use of the suppositories as a routine measure in the preparation of patients for delivery and perhaps in preparation for Cesarean section or hysterectomy. There is no evidence that absorption from the postpartum vagina necessarily indicates absorption in other conditions.

Rock, Barker, and Bacon³ reported from Harvard Medical School on their experiences with the vaginal absorption of penicillin. They concluded that except during the last two months of pregnancy, penicillin is easily absorbed from cocoa butter suppositories in the vagina, giving therapeutic blood levels for from four to six hours. These conclusions were based on nine nonpregnant patients with vaginitis or cervicitis and four patients who were awaiting delivery. Seven recently delivered postpartum patients comprising a third group also showed good blood levels.

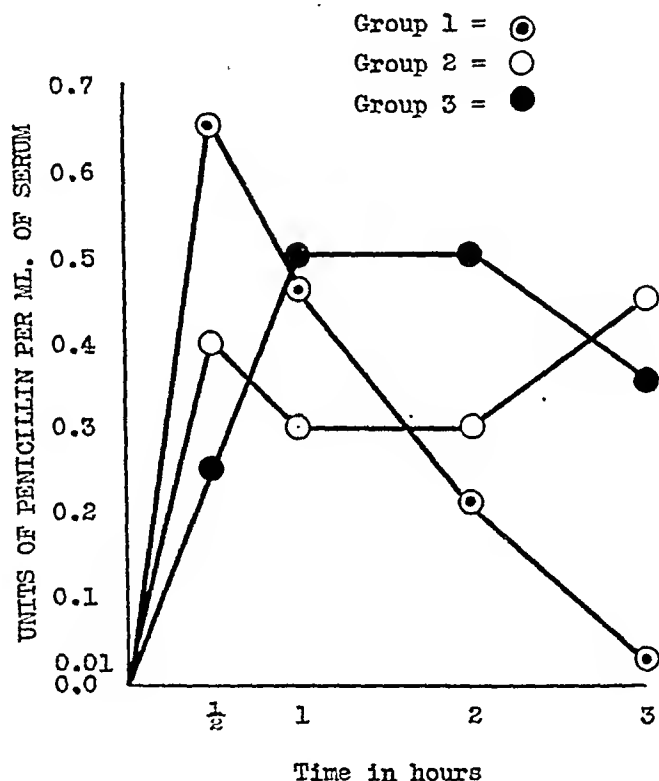


Fig. 1.

Goldberger, Walter, and Lapid⁴ concluded that penicillin in the form of suppositories is readily absorbed through the vagina and that therapeutic levels are easily attained and maintained for at least three hours. These workers used 500,000 units of penicillin. Their average blood penicillin levels at the end of one-half, one, two, and three hours were 0.38 units, 1.35 units, 0.96 units, and 0.38 units respectively. Studies were conducted in ten patients, seven of whom were normal menstruating women. Two were postmenopausal and one was amenorrheic with virilism. All were free of vaginal pathology. Vaginal pH studies were made prior and subsequent to the tests. On studying the table of results, no correlation of the age, menstrual cycle, or the vaginal pH with the levels obtained is apparent. The authors conclude that the vaginal route may be the method of choice for the administration of penicillin in the adult female.

appears that such levels are not dependable following vaginal absorption of penicillin and that intramuscular administration is more feasible.

It is of importance to note that two of the nineteen nurses developed urticaria during the study and two of the patients with vaginitis and leucorrhea developed pruritus only after they had been on treatment some time and after the vaginitis and leucorrhea were much improved. Whether or not the pruritus was caused by the penicillin is problematical.

From our own experiences and those of others reporting recently, vaginal penicillin suppositories are of real value in the treatment of vaginitis. Such value probably stems from the local concentration rather than from the blood level obtained by absorption. The real value of vaginal penicillin suppositories is in the treatment of vaginitis, and the blood levels achieved during such therapy are incidental and of doubtful importance.

Conclusions

1. Penicillin, when administered in cocoa butter suppositories, is absorbed from the vagina under certain conditions.

2. The degree of absorption and the resulting blood penicillin level are subject to great variation and are difficult to predict in any given case. Apparently there is less absorption of penicillin from the normal vaginal mucosa than from the inflamed mucous membrane in a patient with vaginitis.

3. Because of the incidence of side reactions and, because of the unpredictable blood levels obtained subsequent to the use of penicillin vaginal suppositories, it does not seem rational to advocate this route of administration in preference to intramuscular injection or oral therapy when the desired result is the production and maintenance of a therapeutic blood penicillin level.

4. The real value of penicillin vaginal suppositories is in the treatment of vaginitis where the local concentration of penicillin is of prime importance and the production of blood levels is only a matter of secondary interest.

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720 NORTH MICHIGAN AVENUE.

TABLE IV—CONT'D

| NAME | AGE | MENSTRUAL HISTORY | DAY OF CYCLE | BLOOD LEVELS | | | |
|-------|-----|------------------------------|--------------|-------------------|-------|-------|-------|
| | | | | $\frac{1}{2}$ HR. | 1 HR. | 2 HR. | 3 HR. |
| R. B. | 29 | Cycle 28/5 LMP 1/16/47 | 1/21/47 | 0 | 0 | 0 | 0 |
| | | | 1/29/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 5/47 | 0 | 0 | 0 | 0 |
| | | | 2/12/47 | 0 | 0 | 0 | 0 |
| C. G. | 24 | Cycle 28/5 LMP 1/13/47 | 1/ 7/47 | 0 | 0 | 0 | 0 |
| | | | 1/25/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 1/48 | 0 | 0 | IC | 0 |
| | | | 2/ 8/48 | 0 | IC | 0 | 0 |
| W. P. | 22 | Cycle 25/4 LMP 1/22/47 | 1/25/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 1/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 8/47 | 0 | 0 | 0 | 0 |
| | | | 2/15/47 | 0 | 0 | 0 | 0 |
| A. D. | 34 | Cycle 28/4-5 LMP 1/15/47 | 1/20/47 | 0 | 0 | 0 | 0 |
| | | | 1/28/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 4/47 | 0 | 0 | 0 | 0 |
| | | | 2/11/47 | 0 | 0 | 0 | 0 |
| J. K. | 23 | Cycle 28-30/6 LMP 1/20/47 | 1/24/47 | 0 | 0 | 0 | 0 |
| | | | 2/ 3/47 | 0 | 0 | 0 | 0 |
| | | | 2/10/47 | 0 | 0 | 0 | 0 |
| | | | 2/17/47 | 0 | 0 | 0 | 0 |

IC—incomplete hemolysis which is interpreted to represent amounts so small that they were unassayable.

The most recent report is a paper by Schudmak and Hesseltine⁵ of the University of Chicago. Their paper on "The Absorption of Penicillin from the Human Vagina" was read by title at a recent meeting of the Illinois section of the Society of Experimental Biology and Medicine. Although this paper is not available at the time of this writing, one of the authors has informed us through personal communication that vaginal absorption of penicillin as determined by their studies has been inconstant and unpredictable. This has certainly been our experience.

From the literature and from our own results it appears that there is some degree of vaginal absorption of penicillin under certain circumstances. However, the degree of absorption is extremely inconstant and unpredictable. A possible relationship of the vaginal pH and the degree of absorption occurred to us but Goldberger and his workers have not demonstrated any correlation. It seems feasible that the inflamed vaginal mucosa with the accompanying hyperemia incident to vaginitis might be conducive to a degree of absorption different from that of the normal vaginal mucosa in a healthy young patient. In the group of nineteen nurses, all subjects were at bed rest and loss of penicillin from the vagina was kept at a minimum. Tests were conducted by the same method and personnel as applied to our other three groups. The consistent lack of appreciable blood levels of penicillin in this group must be significant.

Goldberger's conclusion that vaginal administration of penicillin may be the method of choice in adult women seems unjustified in the light of our studies, if the production of therapeutic blood levels is the desired result. It

Rationale and Methods

When a radioactive isotope is used in biological research it is mixed with a preponderant quantity of its naturally occurring, nonradioactive isotope; the radioactive substance is employed to tag or label the naturally occurring substance so that the latter may be distinguished from that already present in the body. Thus when radioactive sodium (Na^{24} , i.e., Na with an atomic weight of 24) is used to study the behavior of sodium (Na^{23}) intrinsic to the body, the Na^{24} is present in the sample in an infinitesimally small amount as the chloride together with a weighable amount of ordinary NaCl . The mixture of the two isotopes is referred to as tagged or labeled sodium, and will be designated by the symbol Na^* . In practice, a sample of tagged sodium is weighed and the radioactivity measured in terms of the radiation or counts emitted per second; if the radioactivity of any part of the sample is subsequently known, it is then possible to calculate the corresponding weight of the tagged sodium which is present. We shall present our data in terms of tagged sodium; it will be evident that this refers to sodium (Na^{24} plus Na^{23}) introduced into the body and is not to be confused with the sodium intrinsic to the body. The quantities of tagged sodium used in our experiments were kept as small as were compatible with precise measurements of their radioactivity and were so minute in comparison to the normal sodium content of the body that they are properly called tracer quantities (see Table I).

The fundamental assumption in the use of a radioactive isotope to measure placental permeability is that the radioactive substance crosses the membrane precisely as does its naturally occurring isotope, and therefore, the two isotopes cross the placenta in the same proportion as is found in the fluid bathing it. In the case of the placenta this means that:

$$\frac{\text{Na}_{mp}}{\text{Na}^*_{mp}} = \frac{\text{Na}_f}{\text{Na}^*_f} \quad (1)$$

where Na_{mp} refers to the concentration of normally occurring sodium in the maternal plasma, Na^*_{mp} to the concentration of tagged sodium in the maternal plasma; and Na_f and Na^*_f are the quantities of the corresponding substances transferred to the fetus during the time of an experiment.

Our experimental data have as a first aim the evaluation of Na_f . This quantity divided by the weight of the placenta will be taken as a measure of placental permeability to sodium. Na_f can be calculated from equation (1) if the other three quantities are known. The concentration of sodium in human plasma, Na_{mp} , has been frequently determined, and has an average value of 3.3 mg. per 100 c.c. of plasma.³ The evaluation of Na^*_{mp} is less direct. After injection of a solution of Na^*Cl into a maternal vein the concentration of Na^* in the plasma rapidly diminishes due to its passage into the extracellular fluid of the mother. Since the amount of labeled sodium transferred to the fetus is directly proportional to its concentration in the maternal plasma, only the average concentration in the maternal plasma during the period of transfer is suitable for substitution in the equation. Our first series of experiments, therefore, was designed to measure the rate of disappearance of labeled sodium after its intravenous injection; and from these data the average plasma concentration was obtained. The measure of the quantity of labeled sodium transferred to the fetus (Na^*_f), moreover, is valid for substitution in the equation only if none returns from fetus to mother during the period of observation. It is reasonable to assume that early after introduction of the tagged sodium into the maternal circulation, its concentration in fetal plasma remains so low compared to that of maternal plasma that only a negligible quantity returns from fetus to mother. This condition was taken to be satisfied in the guinea pig⁴ when the concentration of the tagged

THE PERMEABILITY OF THE HUMAN PLACENTA TO SODIUM IN NORMAL AND ABNORMAL PREGNANCIES AND THE SUPPLY OF SODIUM TO THE HUMAN FETUS AS DETERMINED WITH RADIOACTIVE SODIUM

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TO OBTAIN comprehensive information on the permeability of the placenta. One should be in a position, ideally, to measure its permeability to many and diverse test substances. These substances should be closely related chemically and physically to those constituents of the maternal plasma which are normally transferred across the placenta from mother to fetus. The availability of radioactive and stable isotopes, together with exquisitely sensitive and reliable methods for their quantitative measurement, has furnished a method which satisfies this criterion. Because of the chemical identity of these isotopes with their naturally occurring counterparts in the body, we are assured that their biological behavior is normal when the precaution is taken of using radioactive substances in amounts substantially less than that known to produce radiation effects. A molecule may be identified or "marked" with an isotope (e.g., in "heavy water," hydrogen of atomic weight 2 replaces its isotope, hydrogen of mass 1, found in ordinary water) and the molecule subsequently traced by detecting the isotope. Or the isotope may be studied as an ion (e.g., Na^{24} which is radioactive and which is detected by one of several instruments used for measuring radioactivity).

The investigations to be reported here had as their objective the measurement of the permeability of the human placenta to sodium, primarily in normal cases, and, as occasion permitted, in the presence of disease. The observations have been made in twenty-seven women in whom pregnancy was terminated by abdominal hysterotomy before the period of viability or by cesarean section or pelvic delivery at or near term. Ten of these cases were presented in a preliminary report.¹ We entered upon this program with a background of studies on the placentas of animals representing each of Grosser's four morphological types²; we are able, consequently, to consider the results on man from the viewpoint of comparative physiology, and to relate them to the results obtained from other members of the hemochorial group. As in the animals studied, we shall also be interested, at various stages of pregnancy, in the amount of sodium supplied to the human fetus as this is related to the fetal need for sodium during growth.

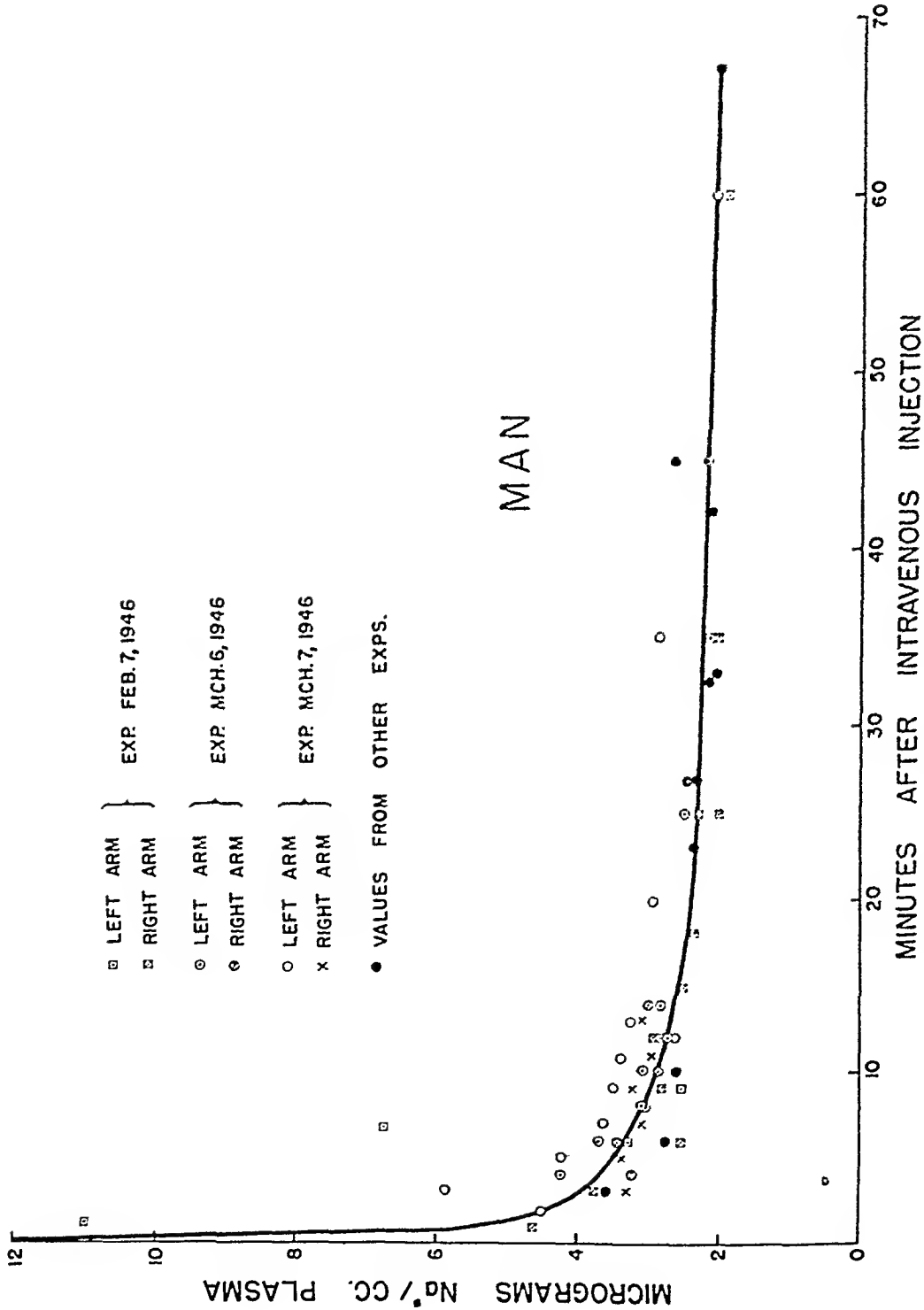


Fig. 1.—Change in concentration of Na⁺ in the plasma with respect to time. The points were adjusted to a standard basis by multiplying them all by a factor which brought the initial concentration to 12 micrograms per cc. of plasma, as explained in the text.

sodium in the fetus (referred to a unit concentration of tagged sodium in the maternal plasma) increased linearly with time. The period of linear exchange in the guinea pig lasts for from two to three hours after injection; the rate of accumulation in the fetus then decreases until equilibrium is reached at about eight hours. Because of experimental limitations we have not been able to determine the period of linear acquisition by the human fetus. To be as certain as possible about procedure, however, delivery of the fetuses has usually been made approximately thirty minutes after injection of the radioactive material. This procedure gave concentrations of labeled sodium in the fetus as related to unit concentration in the maternal plasma well below the ratio for linearity in the guinea pig.

The umbilical cord was clamped as soon as possible, usually within a minute, after incision of the uterus was begun. Immediately thereafter a sample of maternal blood was taken. The fetus and placenta were weighed, the latter being freed of its membranes, cord, and superficial blood. Nonviable fetuses were ashed as previously described⁴; blood samples were secured from viable fetuses one to three hours after delivery. This time interval was chosen to permit equilibration of plasma sodium with extracellular sodium. The radioactivity of the samples of maternal plasma, fetal ash, and of the fetal plasma was then measured and the quantity of tagged sodium present in these samples calculated from the radioactivity. The total quantity of tagged sodium in a viable fetus was calculated from the concentration found in the plasma and from the known volume of the extracellular space which has been found to average 43.5 per cent of the body weight.⁵ The average value for the concentration of tagged sodium in maternal plasma was obtained as will be described below in the presentation of the disappearance curve of tagged sodium from plasma.

The labeled sodium was prepared in the 60-inch cyclotron of the Department of Terrestrial Magnetism, Carnegie Institution of Washington, by deuteron bombardment of metallic sodium. After bombardment, the sodium was dissolved in ethyl alcohol, and Na^*Cl then precipitated with concentrated HCl . Finally an aqueous solution of Na^*Cl was made using distilled water. Appropriate precautions were taken with respect to tonicity, neutrality and sterility of the solution. The amount of tagged sodium injected into an individual averaged about 30 mg. with an activity of 0.3 millieurie. The radioactivity of the samples was measured by a temperature controlled, pressure ionization chamber connected to a string electrometer⁴; these measurements were corrected for self-absorption of radiation by the sample and for the background of the instrument.

Results

The disappearance curve for Na^ in plasma after its intravenous injection.*—As has been pointed out, the calculation of the placental transfer rate for sodium depends upon an accurate estimation of the average maternal plasma concentration of Na^* present during the period of transfer under observation. This entails the description of the change in concentration of Na^* in maternal plasma from the time of its intravenous injection until the time of delivery of the fetus. Multiple sampling of maternal blood at the time of the transfer studies was avoided by establishing a time-concentration curve in advance (Fig. 1). This was accomplished by injecting a known quantity of Na^* into each of three normal, pregnant women. The curve was standardized so that the average concentration for a given pregnant subject could be determined by measurement of the Na^* concentration of a single plasma sample taken at a known time. This

TABLE I. VALUES FROM WHICH THE DATA OF FIG. 2 AND TABLE II HAVE BEEN DERIVED*

| HISTORY NUMBER | INDICATION FOR OPERATION | DELIVERY TIME (MINUTES) | FETAL WEIGHT (GM.) | GESTATION AGE (WEEKS) | PLACENTAL WEIGHT (GM.) | Na ⁺ IN TOTAL FETUS (MICROGRAM) | Na ⁺ /C.C. OF MATERNAL PLASMA | |
|-------------------|-----------------------------|-------------------------------|--------------------------|-----------------------------|------------------------------|--|---|------------------------|
| | | | | | | | FOUND (MICROGRAM) | AVERAGE (MICROGRAM) |
| 103003 | Previous section | 33 | 2700 | 38 | 370 | 700 | 1.49 | 1.94 |
| 247063 | Psychiatric | 27 | 402 | 16 | 126 | 39.0 | 0.97 | 1.31 |
| 231656 | Psychiatric | 30 | 36 | 10 | 63 | 9.5 | 1.29 | 1.74 |
| 249863 | Psychiatric | 32 | 345 | 20 | 156 | 167 | 1.42 | 1.84 |
| 260095 | Previous section | 27 | 2180 | 37 | 214 | 668 | 4.43 | 5.98 |
| 113669 | Twin pregnancy | 28 | 2030 | 40 | 205 | 264 | 4.43 | 5.98 |
| 128414 | Previous section | 28 | 3040 | 40 | 490 | 1230 | 2.67 | 3.60 |
| 376433 | Pelvic delivery | 55 | 3340 | term | 505 | 1120 | 1.34 | 1.60 |
| 389120 | Previous section | 33 | 3430 | 37 | 516 | 760 | 1.69 | 2.20 |
| 311276 | Chorea | 29 | 92 | 14 | 92 | 19.0 | 2.40 | 3.23 |
| 254037 | Previous section | 32 | 2100 | 34 | 370 | 835 | 1.79 | 2.34 |
| 136080 | Pulmonary tbc. | 30 | 4 | 9.5 | 19 | 0.61 | 0.88 | 1.18 |
| 380115 | Pelvic delivery | 30 | 3680 | 40 | 490 | 1240 | 1.60 | 2.16 |
| 399157 | Myoma uterus | 32 | 2790 | 36 | 490 | 1560 | 2.35 | 3.06 |
| 396381 | Contracted pelvis | 31 | 2630 | 36 | 375 | 1080 | 1.92 | 2.59 |
| 406823 | Chr. pyelitis | 46 | 1500 | 31 | 243 | 1120 | 3.00 | 3.80 |
| 408367 | Ca. abdomen | 30 | 152 | 17 | 97 | 67.0 | 2.86 | 3.86 |
| 257328 | Contracted pelvis | 30 | 2490 | 40 | 335 | 1190 | 3.86 | 5.22 |
| 240415 | Epilepsy | 35 | 19 | 12 | 34 | 10.5 | 3.58 | 4.65 |
| 165446 | Chr. nephritis | 31 | 14 | 12 | 34 | 30.4 | 4.33 | 5.84 |
| 250383 | Hypertension | 29 | 129 | 16 | 100 | 74.3 | 2.97 | 4.00 |
| 259938 | Hypertension | 27 | 614 | 24 | 168 | 49.0 | 0.45 | 0.61 |
| 389368 | Hypertension | 28 | 361 | 20 | 140 | 138 | 2.97 | 4.00 |
| 247202 | Hypertension | 31 | 2780 | 37.5 | 455 | 1190 | 2.24 | 3.02 |
| 250393 | Pre-eclampsia | 28 | 354 | 18 | 100 | 7.3 | 0.22 | 0.30 |
| 317603 | Pre-eclampsia | 31 | 1480 | 31 | 220 | 524 | 4.70 | 6.10 |
| 376618 | Cardiac disease | 29 | 247 | 18.5 | 121 | 278 | 2.00 | 2.20 |
| | Cardiac disease | 34 | 201 | 18 | 107 | 64.8 | 1.72 | 2.25 |

*The average concentration of Na⁺ in the maternal plasma for the duration of the experiment has been calculated as explained in the text. Delivery time refers to the interval between i.v. injection of Na⁺ and clamping of the umbilical cord.

was done as follows: For each of the three individuals studied we calculated the plasma concentration of Na^* which could have been present immediately after injection if the injected Na^* had been distributed uniformly in the plasma. A standard plasma volume of 45 c.c. per kilogram body weight was assumed. This initial concentration (which varied among the three subjects but averaged about 12 micrograms Na^* per c.c. of plasma) in each woman was multiplied by whatever factor was necessary to convert it to a standard concentration of 12 micrograms Na^* per cubic centimeter of plasma. Subsequent measurements of plasma concentration in each of the three cases were then multiplied by the same factor. Since the standard plasma volume which has been used as a constant, this treatment is equivalent to relating all concentrations to a constant quantity of Na^* per unit body weight. The average concentration of Na^* in the maternal plasma for a period of thirty minutes after injection was obtained from the standard curve of figure 1 as follows: The area under the curve from zero time to thirty minutes was measured with a planimeter. This area was then divided by the time interval, thirty minutes, to obtain the average altitude, or average concentration. The ratio of this concentration to that found at thirty minutes is the factor, 1.35, by which the concentration of Na^* at thirty minutes in a subject must be multiplied to give the average concentration for that subject. Average maternal values calculated in this way are given in the last column of Table I.

As shown in Fig. 1, samples of blood were taken simultaneously from veins of the right and left arms. This provided a measure of mixing time and it was assumed that mixing was essentially complete when the amount of Na^* in the two samples was about equal. In one subject, the mixing time estimated in this way amounted to about eight minutes; in the second, to twelve minutes; and in the third, to thirteen minutes. The average concentration of Na^* in the maternal plasma will of course be affected by the mixing time. We believe that for our purpose the average concentration in the maternal blood of the placenta differs in no important way from that of the peripheral blood as we have established it.

The normal placental transfer rate for sodium at different gestational ages.—The amount of sodium transferred to a fetus during an experiment was calculated from equation 1. Values for Na^*_{f} and Na^*_{mp} , the latter averaged for the observed period of transfer, are given in Table I. Na_{mp} was taken to equal 3.3 mg. per c.c. The value of Na_{f} derived from these data was finally converted to milligrams of sodium transferred across one gram of placenta in one hour. The results are presented in Fig. 2.

The curve of Fig. 2 has been drawn to fit observations made on individuals in which there was no reason to suspect abnormality of placental function. Sixteen normal cases in this series were distributed among individuals who were delivered abdominally because of previous section, mental disease, chorea, tuberculosis, myoma of the uterus, pyelitis, or carcinoma of the abdomen. In addition there are two cases which have been observed during normal labor and vaginal delivery. Six of these cases fell within the ninth to seventeenth week of pregnancy; ten were between the thirty-sixth week and term; only three came between the seventeenth and the thirty-sixth week because of the rarity of interruption of pregnancy during this period.

Several conclusions of major interest to us are to be drawn from the results. The first is that the apparent permeability of the human placenta to sodium increases about 70 times from the ninth to the thirty-sixth week of gestation. The second is that from the thirty-sixth week to term there was in all but one case a rapid decrease in permeability; this decrease was most marked in a single case of twins. The third is that in the two cases where transfer was observed during normal labor for the half hour or hour preceding delivery, there was no decrease in transfer rate. And finally there was no evident difference between the transfer rates when spinal or caudal anesthesia was used and when general anesthesia was obtained with sodium pentothal or gas-oxygen-ether.

The effect of chronic hypertension, cardiac disease and pre-eclampsia on the placental transfer rate.—Five patients with chronic hypertension were studied, one complicated by chronic nephritis. Three of these were between the twelfth and twentieth weeks of pregnancy, one at the twenty-fourth week and the last near term. They varied in severity from mild degrees of hypertension with blood pressures of 140 to 150 over 90, to severe cases with retinal arteriosclerosis and hemorrhages and blood pressures of 180 over 110 or 120. As shown in Fig. 2, there was no evidence of abnormality of placental transfer in any of these cases.

Measurements were made on two patients with cardiac disease, both in the nineteenth week of pregnancy. In one there was complete heart block, diminished cardiac reserve and considerable vasomotor instability; in the other, rheumatic heart disease with mitral stenosis, a bundle branch block and moderate diminution in cardiac reserve. Both of these individuals had normal placental transfer rates.

Finally, observations were made on two cases of pre-eclampsia. One at a gestational age of eighteen weeks had severe hypertension and albuminuria with retinal hemorrhage and partial retinal detachment. The transfer rate in this patient was normal. The other woman, in the thirty-first week of pregnancy, had edema in addition to severe hypertension and albuminuria. The transfer rate in this case was reduced about 50 per cent; this is the single instance in our series where there has been a definite alteration.

Fetal need for sodium relative to its supply across the placenta.—The ratio of the quantity of a substance supplied to the fetus from the maternal plasma to the amount of that substance retained by the fetus in its growth has been called the safety factor for that substance.⁴ The quantity of sodium transferred to the fetus across the placenta per hour is calculated from equation (1) as explained above. The amount of sodium retained by the fetus in an hour's growth is equal to the fetal weight multiplied by the hourly per cent weight increase of the fetus multiplied by the total sodium in a unit weight of fetal tissue. The safety factor has been calculated for four fetal ages and is given in Table II. The value of the safety factor varies from 160 at a fetal age of twelve weeks to the remarkably high value of 1130 at forty weeks. This means that of 1,130 parts of sodium delivered to the fetal circulation at forty weeks only one part is retained by the fetus in its growth, and 1,129 parts are returned to the maternal circulation.

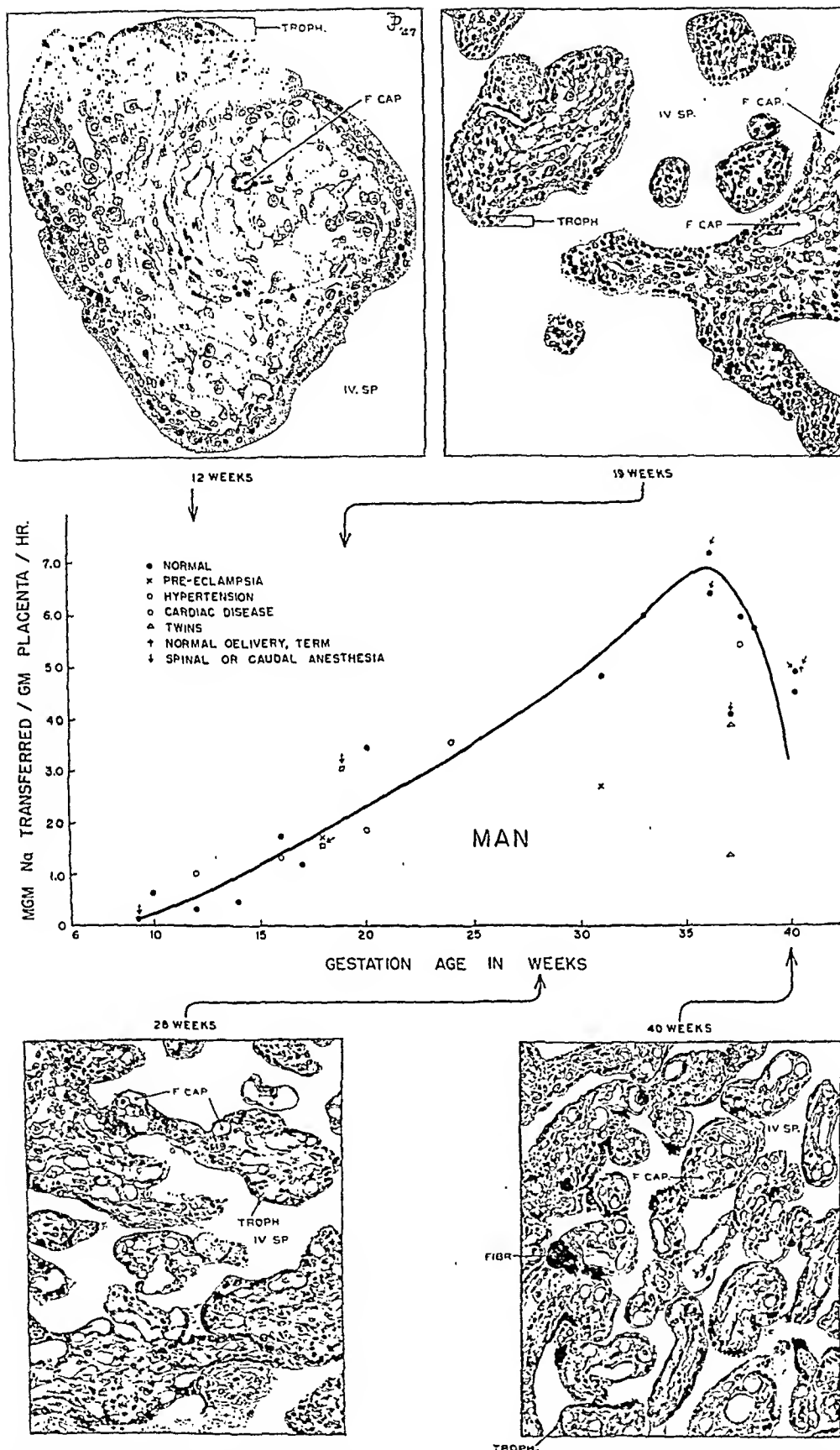


Fig. 2.—Variation of the rate of transfer of sodium with respect to gestation age. The points have been derived from the data of Table I. The camera lucida drawings (X155) are from sections of normal human placentas at the indicated gestational ages and illustrate the histological changes which can be correlated with the change in permeability. Note, as the placenta ages, decrease in thickness of trophoblast (Troph.), increase in surface of villi exposed to intervillous space (IV. Sp.), and increase in number of fetal capillaries (F. Cap.). Fibr., fibrin.

MGM. Na TRANSFERRED/GM. PLACENTA/HR. AT MIDDLE OF 9TH TENTH OF GESTATION

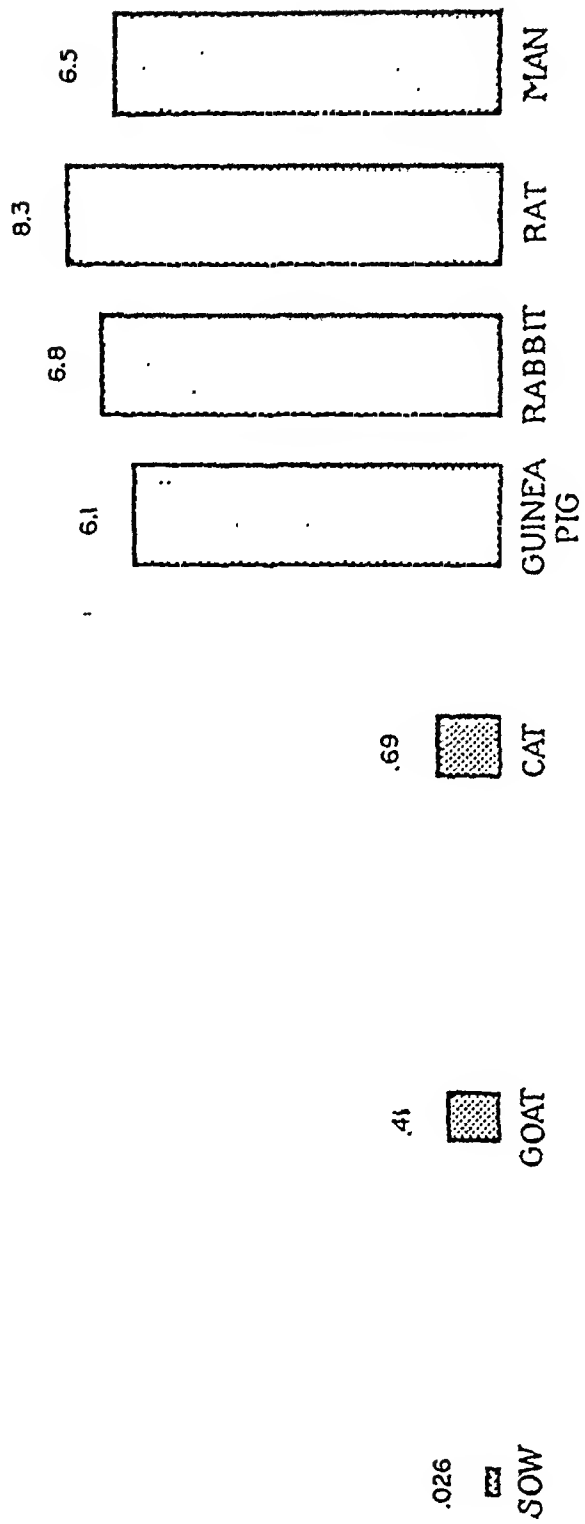


Fig. 3.—Variation of transfer rate of sodium per unit weight of placenta with the morphologic type of placenta. Numerical values give the milligrams of sodium transferred across a gram of placenta per hour as observed in each instance at the middle of the ninth-tenth of pregnancy. The relative magnitudes of the transfer rates are indicated by the relative areas of the dotted rectangles. The diagrams indicate the number and kind of tissue layers interposed between maternal and fetal circulation in each of Grosser's four groups.

TABLE II. FETAL NEED FOR SODIUM RELATIVE TO SODIUM SUPPLIED ACROSS PLACENTA AT VARIOUS GESTATION AGES*

| FETAL AGE (WEEKS) | FETAL WEIGHT (GM.) | TOTAL Na OF FETUS (MG.) | DAILY WEIGHT INCREASE (PER CENT) | TOTAL Na RETAINED DAILY IN GROWTH OF FETUS (MG.) | Na SUPPLIED TO FETUS PER DAY (MG.) | SAFETY FACTOR |
|-------------------|--------------------|-------------------------|----------------------------------|--|------------------------------------|---------------|
| 12 | 18.2 | 21 | 11.5 | 2.4 | 390 | 160 |
| 20 | 259 | 620 | 2.9 | 18 | 5600 | 310 |
| 30 | 960 | 2250 | 1.5 | 34 | 20600 | 610 |
| 40 | 2915 | 5100 | 1.1 | 56 | 63000 | 1130 |

*The daily per cent weight increase has been calculated from the data of Streeter,⁶ and the sodium content of the fetuses is that found by Job and Swanson.⁷

Discussion

As stated in the introduction of this paper, we have been primarily concerned with the following problems: (1) measurement of the permeability of the normal human placenta to sodium from early in gestation to term; (2) comparison of the permeability of the human placenta with that of other placentas of the hemochorial group; (3) measurement of the effects of disease on placental permeability and (4) evaluation of the supply of sodium to the fetus as this is related to the requirement for sodium during fetal growth.

The human placenta, as is true for all the placental types which have been studied with the tracer technique,⁸ undergoes a very considerable increase in permeability to sodium as gestation proceeds. The peak in transfer rate per unit weight of placenta occurs at about the thirty-sixth week when it is approximately 70 times as great as at the ninth week, the earliest case in our series. This peak is followed by a rapid decline in permeability to term. These changes can be correlated with morphological changes which occur in the placenta during the process of aging. The illustrations of Fig. 2 are typical of placentas of twelve, nineteen, twenty-eight and forty weeks of pregnancy. They are all made at the same magnification ($\times 155$) and show clearly some of the important alterations in this organ as gestation progresses. At twelve weeks, the villi are large, relatively few in number and covered with a double layer of cells, the outer, syncytial and the inner, cellular. At nineteen weeks there is an increase in the number of villi, a decrease in their size and Langhans' layer has almost completely disappeared. The increase in total cross sectional area of the villi, together with thinning of their walls, continues through the twenty-eighth week to term. Higher magnification reveals in addition, as pregnancy proceeds, an increase in number of fetal capillaries within the stroma of the villus together with a decrease in the thickness of the capillary walls. The terminal sharp decrease in placental permeability is undoubtedly due in considerable measure to the deposition of fibrinoid over the surface of the villus. All of these morphological changes provide an interpretation of the observed changes in transfer rate per unit weight placenta.

The placenta of man in Grosser's classification² belongs to the hemochorial group as do the placentas of rabbit, rat and guinea pig. According to the results of Mossman,⁹ the rabbit's placenta in the latter stages of pregnancy becomes

Summary

1. Changes in rate of placental transfer per unit weight of placenta have been measured in normal pregnancies, using radioactive sodium, from the ninth week of gestation until term. The permeability of the placenta increases about 70 times during this period. The type of anesthesia was without effect on the rate which was also unaffected during labor immediately preceding birth. The permeability to sodium of the human placenta is like that of other members of the hemochorial group.

2. In a small series of cases, chronic hypertension and cardiac disease were without effect on the rate of transfer. One of two cases of pre-eclampsia showed a marked reduction of permeability.

3. The fetus receives across the placenta at the twelfth week of pregnancy 160 times, and at the fortieth week, 1100 times as much sodium as is incorporated in the growing tissues.

We are grateful to Dr. N. J. Eastman for his interest and generous cooperation.

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hemoendothelial and Mossman suggests that the same change may occur in the placentas of other rodents. Hard,¹⁰ however, has obtained evidence using the phosphatase reaction that the placenta of the guinea pig remains hemochorial throughout gestation. The results on transfer of sodium across the human placenta afford a functional test of its morphological similarity to other members of the hemochorial group. Fig. 3 presents schematically the tissue layers interposed between maternal and fetal circulations in Grosser's four groups. Above the diagrams of the placentas there is indicated graphically the amount of sodium transferred per Gm. placenta per hour at the middle of the ninth-tenth of gestation. It is evident that the four placental types can be readily distinguished from one another by the differences in their permeabilities. It is also evident that the permeability of the placenta of man to sodium agrees closely with other members of the hemochorial group. Once again in our studies on placental permeability, Grosser's classification has proved its extraordinary usefulness in the interpretation and integration of our results.

Our experience with the effect of disease, anesthesia and labor on the permeability to sodium is rather meager and suggests only tentative conclusions. The permeability of the placentas from five patients with hypertension and two with cardiac disease was found to be normal. The transfer rate was independent of the type of anesthesia. Two cases in which transfer rates were measured during labor, just prior to the time of delivery, showed normal rates indicating that placental function is not remarkably disturbed during this period. A reduction of transfer rate was noted in one of two cases of pre-eclampsia and the rate was low in the single case of twins which was studied. In our opinion, more experience with sodium and other tracer materials is needed in these several conditions before reliable conclusions about placental function can be drawn.

The use of tracer substances permits the study of that aspect of fetal nutrition which is concerned with the quality of substances supplied to the fetus as this is related to the growth requirements of the fetus. The lowest safety factor (ratio of the amount of a substance supplied to a unit weight of fetus to the amount of that substance retained by the unit weight of fetus in its growth) for sodium has been observed in the sow and has a value of 3.5.¹¹ The highest safety factor for sodium observed prior to the studies reported here is in the guinea pig and has an average value of 50.⁴ Man, in our experience, is unique in the extraordinarily high value of the safety factor which varies from 160 at twelve weeks to over 1100 at term; less than 0.1 per cent of the sodium which reaches the human fetus at term is retained, 99.9 per cent being returned to the maternal circulation. Man is unique also in that sodium is supplied at a constant rate, about 0.9 mg. per Gm. fetus per hour, from the twelfth week of pregnancy when the fetus is reproducing its weight at the rate of about 12 per cent per day to term when the daily per cent weight increase is only about 1 per cent. This is the single exception which has been found to the hypothesis that the fundamental principle underlying placental function is that the rate at which substances are transferred to a unit weight of fetus shall parallel the relative growth rate of the fetus.⁹

TABLE I. BREECH DELIVERY (500 CASES)

| Total fetal mortality Cesarean or external version | | 13 per cent 26 cases | |
|---|-------|-------------------------|----------|
| | CASES | FETAL MORTALITY | |
| | | NO. | PER CENT |
| Full term | 403 | 31 | 7.6% |
| 8 months | 44 | 11 | 25% |
| 7 months | 27 | 22 | 81% |

Certain conditions in the last trimester demand interruption of the pregnancy. Most obstetric techniques have been simplified during the last few years. But induction of labor has not been appreciably facilitated by improved methods. The obstetrician is frequently faced with the necessity of performing a premature delivery with no "near-perfect" method at his disposal.

TABLE II. INDUCTION OF LABOR BEFORE TERM IN ROYAL VICTORIA HOSPITAL

| | 1941-43 FETAL MORTALITY | | 1944-46 FETAL MORTALITY | |
|----------------------|-------------------------|----------|-------------------------|----------|
| | NO. | PER CENT | NO. | PER CENT |
| Rupture of membranes | 557 | 6.5% | 528 | 6.2% |
| Medical | 340 | 4.5% | 374 | 4.7% |
| Medical & pituitrin | 136 | 5.3% | 116 | 7.0% |
| Bag induction | 34 | 59.0% | 19 | 57.0% |

We are agreed that prophylaxis is the best form of treatment; possible prevention of those conditions which are prone to force induction should be further investigated. A nearer approach to maturity creates a better chance of survival unless some complicating factor outweighs this advantage.

Cesarean section is a quick and sure way of delivery. However, there are several pitfalls, especially in a French-Canadian environment. This operative procedure causes definite limitation to the size of the patient's family. But more important are the dangers of hemorrhage or sepsis which must always be considered. Sometimes this operation is the method of choice. It is the "trump card" only to be used at the proper time.

Delivery per vagina necessitates induction of labor. If the patient is approaching full term, most methods of induction are equally efficient. The difficulty encountered in the induction of labor is usually in direct proportion to the number of days the patient is lacking with reference to her appointed time of delivery. This is easily explained. Necessary stimulation to uterine contraction is lacking. In addition, the thinning of the lower uterine segment has not taken place. Induction of premature labor at any period in the last trimester should only be instigated on account of a definite medical indication. Too frequently labor is induced to please the patient, or even to accommodate the doctor who is in charge of the case.

With reference to cephalopelvic disproportion cases, we do not induce labor unless the degree of disproportion is only moderate and the patient is near full term. Before induction, we make certain of the disproportion by vaginal examination; in addition we ascertain the condition of the cervix

THE BABY AS A PROBLEM IN PREMATURE DELIVERY*

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MUCH emphasis has been placed upon the importance of recognizing dystocia caused by malformation of the pelvic bones. This usually is referable to those cases near term who have a large-sized fetus and where there is a bony disproportion. But when we review figures of fetal deaths, we are impressed by the fact that a great proportion of these deaths occur in small babies where there is no bony disproportion. Soft tissue dystocia plays the important role.

Normal individuals possess a cervical canal which is the valve of the uterus. The cervical function in pregnancy is to hold the products of conception in their normal position. As maturity is approached the valve should release and allow the contents of the uterus to be expelled without causing undue obstruction. This is a gradual process which occurs in those weeks immediately preceding full term. Thinning of this lower uterine segment should normally be a non-painful procedure occurring before the onset of labor.

When labor occurs prematurely there is a great difference. The thick lower segment must be dilated by painful contractions. This is a tedious process and causes greater hazards to an immature fetus. Premature labor is frequently an accidental occurrence; it is unavoidable following some acute crisis or infection. These cases should be handled with extreme care.

The fetal mortality in vertex presentations where the baby is premature ranges far higher than those of mature infants. Complications are varied but the maximum danger occurs in the second stage of labor, relative to pressure of the soft malleable head against the resisting tissues of the pelvic floor. Mortality is still a great deal higher when the fetus presents as a breech, due to the fact that the diameters of the premature baby's hips or shoulders are less than those of the aftercoming head. Consequently, the head becomes compressed by a partially dilated cervix and by a lower tract which has not been adequately distended. A review of 500 breech cases in our Clinic showed interesting results.

Many obstetricians condemn bag induction. I agree that the indications are few. However, if labor occurs with the breech presenting, and the baby is premature of twenty-eight to thirty-four weeks' maturity, a bag induction should be considered as a proper dilator. In seven cases of this type, five live babies were obtained.

*Presented, by invitation, at a meeting of the Philadelphia Obstetrical Society, Feb. 6, 1947.

- 1. Those patients only on diet control experienced as high a fetal mortality as the more severe types taking insulin.
- 2. The high incidence of diabetes plus toxemia due to marked increase in prolan found by White and Hunt could not be substantiated. Only 12 per cent of our cases showed evidence of toxemia.
- 3. Normal deliveries were usually postmature and were accompanied by the highest fetal mortality. Labor induced before term gave better results. The lowest mortality (8.3 per cent) was in the group where a cesarean was done before term.

TABLE III. DIABETES MELLITUS (RABINOWITCH)

| Relationship Between Mode of Delivery and Fetal and Neonatal Mortality. (64 deliveries in Montreal) | | | | | | |
|--|------------|--------|----------|------------|--------|----------|
| MODE OF DELIVERY | PRIMIPARAS | | | MULTIPARAS | | |
| | NO. | DEATHS | | NO. | DEATHS | |
| | | NO. | PER CENT | | NO. | PER CENT |
| Natural | 3 | 2 | 66.6 | 13 | 4 | 30.7 |
| Labor induced before term | 11 | 2 | 18.1 | 4 | 1 | 25.0 |
| Cesarean section | 9 | 1 | 11.1 | 24 | 2 | 8.3 |
| Total: | 23 | 5 | 21.7 | 41 | 7 | 17.1 |

Many authors include syphilis as a common cause for prematurity. There have been 512 proved syphilitics in our obstetric service during the last thirteen years: this is an incidence of approximately 2 per cent. Practically every case has received adequate treatment during pregnancy. This is possibly why we do not see many premature babies due to syphilis. We had only three premature babies from syphilitic mothers in 1946. There were forty-one active syphilitics during the year. All cases had received antisyphilitic treatment.

The Baby

We have prepared certain charts which are self-explanatory. Table IV gives the general maternal and fetal mortality. During the six-year period from 1941 to 1946 there were 572 fetal deaths, and the clinical diagnosis is tabulated. Two hundred six of these deaths occurred in premature babies, an incidence of 36 per cent. The more accurate pathologic diagnosis is listed for 286 cases who had autopsy examinations. These excluded those cases where the infant was badly macerated and those where autopsy examination was refused by the parents. Of the 286 cases where autopsies were performed, 58 per cent occurred in premature babies:—

TABLE IV. 1941-1946

| | | |
|--------------------|--------------|------|
| Total deliveries | 15,691 | |
| Maternal mortality | 1941 to 1943 | .17% |
| | 1944 to 1946 | .11% |
| Fetal mortality | 1941 to 1943 | 3.7% |
| | 1944 to 1946 | 3.5% |

Clement Smith and others have shown that the premature baby differs greatly from the full-term infant. There is excessive accumulation of organic acids in the blood. Renal immaturity decreases kidney function, and there is a limitation of water available for urinary secretion. Hepatic immaturity

and make certain that it will not offer too much obstruction. Simple rupture of the membranes is the method of choice except when there is marked disproportion and delivery by cesarean section is indicated.

Toxemia is fairly frequent in our hospital. Most of these cases are referred from outlying districts where they have had inadequate or no prenatal instruction. Prevention of the disease is the best approach when it is possible. Frequent antenatal visits and proper supervision are most essential. We heartily agree with Dr. Winslow Tompkins, in regard to high protein intake with reference to the prophylaxis and treatment of toxemia. Supportive treatment varies little from other clinics.

Induction of labor is carried out only when indicated. It is usually by simple rupture of the membranes. If the patient is severely toxic and she is not near term, we sometimes use the intraovular insertion of a small rubber bag of approximately 150 c.c. content. We fully realize that this type of delivery creates a possible 50 per cent fetal mortality. Cesarean section is occasionally performed for combined indications, and in the nephritic type of toxemia where future pregnancies do not promise any better fetal results.

Placenta previa and fetal mortality go hand in hand. Maternal hemorrhage causes fetal anoxia; there is the additional factor that prematurity also plays a role in producing a delicate baby. Even suspect cases are examined in the operating room. This is to prevent additional or needless loss of blood. The marginal type is most commonly treated by simple rupture of the membranes. More pronounced types of placenta previa are delivered by cesarean section. Anoxia in the baby is a frequent sequela of maternal blood loss. This is best treated by transfusing the mother with whole blood before operative procedures are instigated. This should be repeated as frequently as indicated. Administration of oxygen to the mother during operation is very beneficial.

Space does not permit discussion of Rh iso-immunization. Induction of labor or, sometimes, cesarean section before the baby becomes overwhelmed with antibodies is the wise procedure. Antibody studies can now give a fairly definite prognosis in most cases. A marked rise or variation in the agglutinating or blocking antibodies is indication for interruption of pregnancy any time after the baby is viable.

In June, 1946, Rivett reported successful results in hydramnios cases by means of repeated aspiration of fluid from the amniotic cavity. This is done through the abdominal wall with little risk. We have completed three cases since that time. One baby is normal, another had marked "clubfeet" and absence of several fingers and toes, while the third was a marked microcephalic with patent ventricular septum. This procedure is only indicated when the fetus is considered normal but small. If the development is not sufficient to assure viability, sometimes aspiration of excess fluid will enable the baby to reach the viable period.

Diabetes complicating pregnancy is a cause for worry. Fetal mortality is very high even in the controlled patient. Rabinowitch points out several important facts:—

Clysis of plasma or glucose and saline is given for dehydration or to stimulate weight gain. The hemoglobin is estimated at least every seven days. Iron therapy is given when indicated. Whole blood transfusions are used when conditions warrant; this is a fairly common procedure in the premature nursery, and the indications have become more numerous.

Our premature nursery has completed three years in operation. For this reason I have taken two three-year periods for comparison. These periods are 1941 to 1943 and 1944 to 1946, inclusive.

The most significant improvement is in the fewer number of deadborn infants in the period from 1944 to 1946. General fetal mortality as well as premature deaths have decreased slightly. It should be emphasized, however, that the incidence of complicated cases has increased considerably in the last three years in our clinic. This is due to the fact that outside doctors would rather not handle this type of case and they are referred to our hospital. For example our admissions of hemolytic disease of the newborn have increased over 200 per cent.

Many of the deaths could not be prevented, but a great number are included which should be considered as preventable. It is interesting to note that only three babies died from effects of syphilis. There were 209 active syphilitics delivered in this series. Only six did not receive antisyphilitic treatment.

TABLE V. PREMATURE BABIES WEIGHING 1,000 TO 2,500 GM.

| | |
|---|--------------------|
| Total number | 912 |
| Incidence | 5.7% |
| Mortality | 1941 to 1943 24.3% |
| | 1944 to 1946 21.0% |
| Five (5) babies under 1,000 gm. survived. | |

TABLE VI. SUMMARY OF INFANTS UNDER 1,000 GM. AT BIRTH

| CASES | BIRTH DATE: | BIRTH WEIGHT (GRAMS) | DISCHARGE DATE: | DISCHARGE WEIGHT: (GRAMS) |
|--------------|-------------|-------------------------|-----------------|---------------------------------|
| 1. Baby S. | Oct. 6/44 | 660 | Feb. 13/45 | 2340 |
| 2. Baby Bl. | Dec. 10/44 | 940 | Mar. 1/45 | 2400 |
| 3. Baby Bll. | Dec. 10/44 | 900 | Mar. 1/45 | 2340 |
| 4. Baby D. | Aug. 2/45 | 930 | Nov. 29/45 | 2340 |
| 5. Baby P. | Sept. 15/46 | 990 | Dec. 21/46 | 2660 |

The premature babies were classified only as those between 1,000 to 2,500 Gm. This coincided very well with estimation from the twenty-eighth to the thirty-sixth week of pregnancy. However, there were seventeen babies admitted to the premature nursery, and they all weighed less than 1,000 Gm. Five of these infants are still alive; the smallest weighed 660 Gm. at birth and it is now over two years of age. This is particularly significant in view of the fact that Haas reports only fifty-seven cases in the literature which survived and also weighed less than 1,000 Gm. at birth.

causes decreased liver function. Blood studies show a comparative anemia with a predisposition to developing anoxia and hemorrhage in the brain and liver. The immature lung is frequently associated with patchy atelectasis which predisposes to subsequent respiratory infection. Altogether the premature baby is a liability.

Antenatal pediatrics is a new term, but the significance is old. We are all agreed that the general physical condition of the pregnant woman is often reflected in the condition of the offspring. This is especially true relative to the premature baby. Prophylaxis of preventable conditions frequently is assured by means of adequate antenatal care. Nutrition is important in all cases. Abnormal findings should be heeded and the complication should be promptly treated. Judicious use of sedatives during labor, type of delivery and well-chosen anesthetic all play an important role in the result obtained.

It has been shown that the incidence of premature infant mortality varies inversely to the size of the babies. We also emphasize the fact that deaths in premature infants become progressively less frequent with each hour of life. Over 50 per cent of all neonatal deaths in premature babies occur during that first twenty-four hours following delivery. Some of these deaths are preventable. This is relative to: conditions caused by anoxia, aspiration of mucus or other fluids, insufficient incubation, and too many contacts.

The obstetrician and pediatrician should work in harmony. Their combined invaluable experience is most essential to obtain good results. This necessitates more than an average knowledge relative to the care of the newborn baby; both obstetric and pediatric interns should receive adequate instruction in the care of the newborn baby. Beck has pointed out the advantages of a definite system. It has also been emphasized in the report of the Illinois State Plan where excellent results were obtained by developing an organization which is supervised jointly by the obstetrician and the pediatrician.

It should be emphasized, however, that the authority and interest of the obstetrician must be maintained in the care of the newborn infant. This is essential due to the fact that effects of pregnancy, labor, and delivery play the major role in the eventual outcome of the offspring. Most fetal deaths occur during that period when the obstetrician is in complete charge, regardless of what system is followed during the neonatal period.

Our hospital has a staff pediatrician who supervises the routine in all nurseries. A resident who is trained in the care of the newborn is in charge of all babies. He reports to the staff pediatrician as well as to the obstetrician who is in charge of the individual case. This resident is present at all difficult deliveries such as cesarean births, difficult forceps cases, and those complicated by placenta previa or toxemia. He supervises and treats all babies from birth until the time of discharge.

Treatment of the premature baby is most important. There are two phases: (1) First hour of life, and (2) Neonatal period in the nursery.

Very small babies are fed every two hours. Poor feeders have a three-hour schedule, and good feeders receive feedings every four hours.

dication for interrupting pregnancy, but prefer to do an abdominal delivery. We prefer it because we have found that more infants survive such a method of delivery, yet the maternal risk has not been increased. We shall continue to do this, under these circumstances, until and unless methods can be developed for inducing and obtaining premature labors that are superior to current ones.

DR. PHILPOTT (closing).—I think Dr. Bachman and I are in agreement with regard to induction of labor and the results thereof. I would only like to define our attitude in Montreal regarding inducing labor. We are in a predominantly French Canadian community and that must be borne in mind. My reaction to cesarean section is that a good many can do one or two cesareans, but not eight or nine in the same patient. Our community is very orthodox in religion. They do not believe in ligation of the tubes and we do not do more cesareans on that account. One or two cesareans can be done safely, but beyond that it is dangerous. Over 50 per cent in the community are Roman Catholics. Most will not consent to ligation of the tubes, and it is necessary to follow the course I have presented, and we have resorted to that. The fewer labors we induce the better results we will get. The premature baby is another problem. It is often a sick baby, it has gone through a tedious labor, and as a result of premature delivery is not fully developed, the renal system and the various other systems are immature, and all in all it is an entirely different problem from the full-term baby. With reference to Dr. Montgomery's question, we have been very painstaking and definite about prematurity.

Our premature mortality rate is slightly higher than figures given by the Long Island College Hospital and the Hahnemann Hospital of Philadelphia. But we have had better success with the very small babies. We cannot boast of a great reduction in mortality during the last three-year period seeing that it dropped only 3 per cent. However, the reduction is important due to the fact that incidence of complicated cases in our clinic has increased considerably during this three-year period. In addition, it should be mentioned that several babies were considered as nonviable in the 1941-43 period. There were 20 babies which were approximately 1,000 grams but they were not weighed. These died shortly after birth, and several of them were indexed as nonviable. In the period from 1944-46 all babies were weighed and the uncorrected mortality includes every baby weighing between 1,000 and 2,500 grams.

Summary

1. Induction of premature delivery should be carried out only on account of a definite indication.
2. Adequate equipment and trained personnel are essential for a premature nursery.
3. Breast milk bank and blood bank facilities are useful adjuncts.
4. Fetal mortality can best be improved by the combined efforts of the obstetrician and pediatrician.

We are grateful for the cooperation and suggestions of Dr. Graham Ross, Pediatrician-in-charge.

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Discussion

DR. CARL BACHMAN.—I wish to emphasize the notion that the premature infant is handicapped not only by its prematurity, but also by the fact that, in the great majority of instances, it is also an ill or damaged infant. Of the factors which militate against its survival, its prematurity per se is perhaps the least important.

The pathologic factors are twofold. The first is the disease or abnormality of the mother, or of the ovum itself, which is responsible for interrupting the infant's intrauterine development prematurely. Who can say that the fetus of a toxic mother, or of one who suffers an antepartum placental hemorrhage, is not likely to be handicapped by these factors? Yet if one reviews one's experience with premature delivery, one must be struck by the fact that the overwhelming majority of them occur, whether spontaneously or by design, because of abnormalities of this character accompanying the gestation.

The second factor is the frequently tedious, and therefore often traumatic character of premature labor and delivery. Some of the factors which make it so have been mentioned by Dr. Philpott. Because of them, our Staff at the University of Pennsylvania have become increasingly loath to resort to induction of premature labor when there is a legitimate in-

Case Reports

CASE 1.—E. P. The patient, a Negro female, gravida i, para 0, whose last menstrual period was Nov. 23, 1944, was admitted to Charity Hospital on July 25, 1945, with the chief complaint of pain in the lower abdomen, and vomiting. When she was three to four months pregnant, the patient had an attack of severe lower abdominal pain associated with fainting from which she recovered spontaneously.

The patient's blood pressure was 135/100. Her abdomen was the size of an eight months' pregnancy, and fetal parts were quite superficial. The abdomen was markedly tender. Fetal heart tones were 140 in the left lower quadrant. Sterile vaginal examination was done. The cervix was pushed forward, soft, long, and patulous. Membranes or fetal parts were not felt through the cervical os. A shoulder was felt posterior to the cervix. Urinalysis was negative. Hemoglobin was 10 grams. X-ray revealed cephalic presentation with back to right. No uterine shadow was seen.

Preoperative diagnosis: abdominal pregnancy.

Laparotomy was performed on July 25, 1945. Uterus was found to be the size of a ten weeks' pregnancy, with a 5 cm. fibroid extending to the left. A male infant was free in the abdominal cavity without a sac. A small amount of fluid was found in the abdominal cavity. Male baby weighed 4 $\frac{3}{4}$ pounds, and had a deformed head and clubfeet. He was in poor condition after birth and died the same day. The cord was tied off close to the placenta and the abdomen was closed without drainage, leaving the placenta in situ.

Postoperative course was afebrile after the first day, and the patient was discharged on the seventeenth day, at which time the placental mass had not regressed in size.

Patient was readmitted on Feb. 7, 1946, with the chief complaint of pain in the abdomen. She was afebrile during the stay in the hospital and was operated on Feb. 19, 1946, for removal of retained placenta. The placenta was found to be attached to the cul-de-sac, posterior surface of the right broad ligament, lateral wall of the pelvis, posterior pelvic wall, rectosigmoid, and mesoappendix. In order to remove the placenta it was necessary to do a subtotal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy. The patient was discharged on Feb. 28, 1946, in good condition.

CASE 2.—V. R. The patient, a 28-year-old Negro female, whose last menstrual period was April 1, 1946, was admitted to Charity Hospital on Jan. 8, 1947, with a history of recurrent abdominal pains every two to three minutes, nausea, and vomiting. On September 17 the patient had an episode of bleeding. Since September, 1946, she had been having periodic attacks of pain in the lower abdomen more severe on the right side, which were relieved by vomiting and aggravated by any activity. The patient said that she felt the baby move only on the right side.

Blood pressure was 110/80. Heart and lungs were negative. Abdomen was enlarged to the size of a term pregnancy, vertex presentation, head floating. Fetal heart tones were best heard in the right lower quadrant, and their rate was 152. The patient was recorded as having hard pains every three minutes. Urinalysis was essentially negative. Hemoglobin was 9.5 grams.

Diagnosis of breech presentation was made which was confirmed by x-ray. X-ray also showed a peculiar shaped occiput in left flank.

On Jan. 9, 1947, the cervix was found to be soft, long, and would barely admit one finger. Exploration of uterine cavity revealed no membranes nor fetal parts. It was found to be about 10 cm. long.

THE FATE OF THE LIVING VIABLE BABIES IN EXTRAUTERINE PREGNANCIES

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THIS paper was written with the idea of determining, as nearly as possible, from the limited clinical material available at Charity Hospital of Louisiana, at New Orleans, and from a survey of the literature the fate of the viable babies delivered from extrauterine pregnancies. Only cases of twenty-eight or more weeks' gestation with babies born living were selected. Forty-one additional cases of living, viable babies in abdominal pregnancies are presented graphically from the literature to supplement those recorded by Sittner,⁶ Hellman and Simon,² and Mitra.⁴ Four new cases are presented from Charity Hospital, at New Orleans, in addition to those recently reported by Beacham and Beacham.¹

Winkel⁷ in discussing the deformities of extrauterine pregnancies stated that 75 per cent of all the deformed children included deformities of the head, half of them deformities of the lower extremity, and 40 per cent deformities of the upper extremity. The more sheltered thorax, abdomen, and genitourinary system were deformed in only 3 or 4 per cent of the babies. Of 316 living, viable babies reviewed by Hellman and Simon² in 1935 from the world literature, including those previously reported by Sittner, a specific statement as to the development of the babies was made in only sixty-four cases. Of these, thirty, or 46.6 per cent, were found to be deformed. One hundred fifty, or 44.3 per cent, of the babies survived for eight days or more, and of these a specific statement as to the development was made in forty-one babies; fifteen, or 36.6 per cent, were found to be deformed. Stabler,⁵ in 1938, reviewed 266 cases from the world literature. Of 266 living, viable babies delivered from abdominal pregnancies, 152, or 57.1 per cent, lived for eight days or more. The fate of only one was undetermined. Twenty-eight, or 10.5 per cent, of these babies were recorded as being deformed. Lelling,³ in reviewing 106 cases in 1938, found that development was mentioned in only 82 of the 106 babies. Of these, thirty-two, or 39 per cent, were recorded as deformed. Mitra,⁴ in reviewing the world literature on advanced extrauterine pregnancies in 1942, found that of 179 extra-uterine pregnancies of more than five months' gestation only 23.5 per cent delivered living, viable babies. Of these, a specific statement as to the development was made in thirteen, ten of which were recorded as being deformed. Beacham and Beacham,¹ in a report of twenty abdominal pregnancies from Charity Hospital, at New Orleans, found that only three, or 15 per cent, delivered living, viable babies.

In our review of forty-one additional cases in the literature we found that a specific statement as to the development was made in thirty-one babies. Twelve, or 38.7 per cent, of these babies were found to be deformed. Ten, or 24.3 per cent, of the babies died before the eighth day.

Four new cases of extrauterine pregnancies with living, viable babies are reported from Charity Hospital.

TABLE I. SUMMARY OF CASES SINCE 1930

| DATE OF OPERATION | OPERATOR | PLACE OF OPERATION | RESULT TO MOTHER | STATUS OF FETUS | SPECIAL NOTES; BIBLIOGRAPHY |
|-------------------|-------------------|--------------------------|-----------------------------|---|--|
| Feb. 2, 1930 | Reeb | Strassburg, Germany | Recovered | 32 weeks; lived; normal | Kries, J. Heb.; Franc. de Gynec. et Obst. 32: 89, 1937. |
| Dec. 29, 1930 | LaRoque | Richmond, Va. | Recovered | 40 weeks; lived; normal | Ware, H. H.; New York State J. Med. 36: 193, 1936. |
| Mar. 1, 1931 | Gushue and Taylor | Tahoku, Formosa | Died (from ileus and shock) | 44 weeks; female, well formed, normal, 7 lbs. | Gushue-Taylor; Brit. M. J. 1: 640, 1942. |
| Apr. 16, 1932 | McNeile | Los Angeles, Calif. | Recovered | 28 weeks; living; no deformities | McNeile, L. G.; West. J. Surg. 45: 119, 1937. |
| Dec. 11, 1932 | Beal and Cassell | Gendur, South India | Recovered | 40 weeks; gasped and died; deformity of left foot; 7 lbs. | Beal, A. M., and Cassell, N. S.; J. Iowa M. Soc. 30: 415, 1940. |
| Sept. 6, 1933 | Ziegler | Pittsburgh, Pa. | Recovered | 40 weeks; living male, normal, 7 lbs. 2 oz. | Eiseman, J. B., and Ziegler, C. E.; J. A. M. A. 104: 2175, 1935. |
| July 20, 1934 | Eula and Eno | Shanghai | Died | 40 weeks; asymmetry of head; deformity of right knee; female, 7 lbs. 8½ oz. | Eno, E., and Towers, A. E.; Chinese M. J. 51: 53, 1937. |
| Jan. 9, 1935 | Woods | Augusta, Ga. | Died (14 hr.) | 38 weeks; living; normal, 5 lbs. 2 oz. | Woods, L. B.; Am. J. Obst. & Gynec. 32: 155, 1936. (Autopsy done.) |
| Feb., 1935 | Bondurant | Cairo, Ill. | Recovered | 40 weeks; living, normal, 4½ lbs. | Bondurant, P.; Illinois M. J. 71: 480, 1937. (Combined full term; extra and intrauterine gestation. Intrauterine child had congenital syphilis; weight 3½ lbs.; lived 5 days.) |
| April 15, 1935 | McNeile | Los Angeles, Calif. | Recovered | 24 weeks; lived 24 hours; normal | McNeile, L. G.; West. J. Surg. 45: 119, 1937. |
| June 11, 1935 | Wilson | Dublin, India | Recovered | 32 weeks; lived; normal, 5¼ lbs. | Wilson, A. S.; Proc. Roy. Soc. Med. 29: 1651, 1936. |
| Sept. 11, 1935 | Anderson | Lucknow, India | Recovered | 4 weeks; lived 15 min.; 6 lbs. | Anderson, M.; Brit. M. J. 2: 589, 1936. |
| Sept. 11, 1935 | Colistro | Pasteur Hospital Uruguay | Died | 40 weeks; baby alive at operation | Colistro; Arch. Frang. de Med. chir. y Especialid 14: 141, 1939. (Did not say if baby continued to live.) |
| Dec. 3, 1935 | MacGregor | Brooklyn, N. Y. | Recovered | 38 weeks; living; not normal, 2,600 gm. | MacGregor, A. S.; Am. J. Obst. & Gynec. 31: 1030, 1937. |

Patient had a laparotomy on Jan. 9, 1947, with preoperative diagnosis of abdominal pregnancy. When the abdomen was opened, the fetal sac was found in the abdominal cavity. This was opened and a living, male infant weighing 6 pounds was delivered by breech extraction. The baby had a plastic deformity of the head and a right clubfoot, and contraction deformities of both arms. The placenta was attached to the bowel, the omentum, and the left cornual portion of the uterus. The placenta was removed with minimum amount of bleeding. The abdomen was closed without drainage.

Postoperative course was essentially afebrile. Five-month check-up revealed that both mother and baby were getting along well.

CASE 3.—E. McC. The patient, a 23-year-old Negro female, gravida i, para 0, whose last menstrual period was June 7, 1946, was admitted to Charity Hospital on March 23, 1947, with the chief complaint of pain in the abdomen for the past two days.

The heart and the lungs were negative. The abdomen was that of a breech at term. Fetal heart tones were 140 and best heard in left upper quadrant. There was marked costovertebral tenderness. During her stay in the hospital, the patient developed enlargement of the abdomen with marked dyspnea.

Vaginal examination disclosed the cervix undilated and uneffaced. No membranes nor fetal parts were felt through the pelvis.

Temperature was 101° F., pulse 130; blood pressure 130/72. Urine was essentially negative. Hemoglobin was 11.8 grams. X-ray revealed one fetus outside of pelvis, breech presentation. No uterine wall could be made out.

Preoperative diagnosis: Abdominal pregnancy at term.

Patient had a laparotomy performed on March 25, 1947, at which time the placenta was found attached to the left cornual portion of the uterus. Some uterine muscle fibers extended up alongside of the fetal sac, but did not entirely cover it. When the sac was opened, it was found to be made up of three definite layers; the outside one was rather fibrous in character. The sac was opened and an 8 pound 15 ounce apparently normal living male child was delivered, who died in a few minutes. In order to remove the placenta, a left salpingo-oophorectomy and supracervical hysterectomy were necessary. The mother was discharged in good condition on the tenth postoperative day.

CASE 4.—D. T. The patient, a 29-year-old Negro female, gravida v, para iii, had not menstruated since her last pregnancy in 1946. She was admitted to Charity Hospital on May 9, 1947, with a history of having had convulsions that morning and having had some sedation given her by her private physician. On admission she was semistuporous and complained of pain in the lower abdomen. She had a productive cough and expectorated blood-tinged sputum. She had been dyspneic for some time.

Temperature was 99.4° F.; pulse 160; blood pressure 164/128. There was marked edema of legs and moderate edema of anterior abdominal wall. The lungs had a few râles at both bases. The heart was enlarged 3 cm. to the left midclavicular line. The abdomen was the size and contour of a term pregnancy. No definite fetal heart tones were heard.

At vaginal examination the cervix could not be felt because it was high and anterior. There was a firm mass about 10 cm. in diameter filling the cul-de-sac.

The urine showed three plus albumin; hemoglobin 11.5 Gm.; venous pressure 115 millimeters of water. X-ray revealed a fetus lying between transverse and in a breech. An electrocardiogram was strongly suggestive of myocardial disease. Kline test was positive.

TABLE 1—Cont'd

| DATE OF OPERATION | OPERATOR | PLACE OF OPERATION | RESULT TO MOTHER | STATES OF FETUS | SPECIAL NOTES; BIBLIOGRAPHY |
|-------------------|---------------------|-------------------------------|------------------|---|--|
| Oct. 4, 1939 | Nicholls | Norfolk, Va. | Recovered | 40 weeks; male, normal, 10 lbs., 3 oz. | Nicholls, R. R.: AM. J. OBST. & GYNEC. 42: 341, 1941. |
| Feb. 25, 1941 | Lin | Poochow, Fukien | Recovered | 40 weeks; lived 2 hr.; asymmetrical face, right elbow; knee could not be straightened | Lin, A. Y.: Chinese M. J. 62: 383, 1945. |
| July 26, 1941 | Slatover | Manchester, England | Recovered | 40 weeks; lived; normal female, 8 lbs., 10 oz. | Slatover, M. L.: Brit. M. J. 1: 669, 1942. |
| Sept. 30, 1941 | Guerrero and Hughes | New Orleans, La. | Recovered | 32 weeks; living | Jecham, W. D., and Beacham, D. W.: Obst. & Gynec. Survey 1: 777, 1946. (L41-42400, Case XII.) |
| Oct. 1, 1941 | Strumpf | Jacksonville, Fla. | Recovered | 29 weeks; living; full term? | Strumpf, I. J.: AM. J. OBST. & GYNEC. 45: 350, 1943. |
| Dec. 31, 1941 | Lucas | Walsall, England | Recovered | 34 weeks; lived; normal male, 7 lbs., 10 oz. | Lucas, C. F.: Brit. M. J. 1: 722, 1942. |
| Mar. 6, 1943 | Rabago | General Hospital, Mexico City | Recovered | 28 weeks; twins, one in uterus; one in cul-de-sac; female in cul-de-sac lived | Rabago: Cir. y. Cirujanos 12: 27, 1944. |
| Dec. 18, 1943 | Rose | Miami, Fla. | Recovered | 34 weeks; lived; normal; 5 lbs., 2½ oz. | Rose, M. J.: J. Florida M. A. 31: 475, 1945. |
| Mar. 7, 1944 | Greene | Memphis, Tenn. | Recovered | 40 weeks; lived only short period | Greene, G. G.: South. M. J. 38: 747, 1945. (Case No. 3.) |
| Feb. 19, 1945 | Morgan and Keovil | Newport, Montreal | Recovered | 36 weeks; lived 1 hr.; male | Morgan, R. G., and Keovil, N. L.: Brit. M. J. 2: 649, 1945. |
| June 7, 1945 | Goodin | Fort William Ontario | Recovered | 40 weeks; male, 7 lbs.; lived 21 hr.; died of atelectasis | Goodin, P.: Canad. M. A. J. 54: 483, 1946. (Baby was a livid-grey color and could not be made to cry.) |
| July 8, 7 | Novey | Baltimore, Maryland | Died | 40 weeks; living; marked bilateral deformities of feet; weight 5 lbs., 8 oz. | Novey, M. A.: Surg., Gynec. & Obst., 66: 671, 1948. (Case 4, A. R., Negro, aged 34 years.) |

| | | | | | |
|----------------|-----------------------|-------------------------------|-----------|---|---|
| Feb. 1, 1936 | Lailey | Toronto, Canada | Recovered | 44 weeks; lived; had one club-foot; no other deformity; 11 lbs. 1 oz. | Lailey, W. W.: Canad. M. A. J. 36: 67, 1937. |
| Mar. 12, 1936 | Lelling and Lendemann | Barbarakranke, Germany | Died | 7 mo.; not resuscitated; club-foot | Lelling, E.: Zentralbl. f. Gynäk. 62: 2209, 1938. |
| Mar. 23, 1936 | Shen Shi Ying | Shanghai | Recovered | 48 weeks; died in 6 hr.; head asymmetrical; cleft palate | Eno, E., and Towers, A. E.: Chinese M. J. 51: 33, 1937. |
| June 7, 1936 | Hoffman | Charleston, West Va. | Recovered | 40 weeks; lived 1½ hr.; baby cyanotic; 4 lbs. 10¾ oz. | Hoffman, W. E.: West Virginia M. J. 33: 496, 1937. (Child has a marked distortion of head; nose is flattened against face, and right nares is closed; flexion deformity of right elbow; right foot is everted.) |
| June 25, 1936 | Sulamanen | Mexico City | Recovered | 39 weeks; lived 17 hr.; 6 lbs. 2 oz. | Salamauea, A. G.: J. Internat. Coll. Surgeons 3: 271, 1940. |
| May 1, 1937 | Bruck | Grunberg | Recovered | Living; normal; 3,300 Gm. | Stavenhagen, Med. Klin. 33: 1609, 1937. |
| June 10, 1938 | Harkness | Mevanza, Tanganyika Territory | Died | 40 weeks; not resuscitated; normal, 7½ lbs. | Harkness, J., and Fairfax, B.: Brit. M. J. 2: 1044, 1938. (There was question if baby was living. Mother died at surgery. Head slumped into vagina.) |
| Aug. 27, 1938 | Hamblen | Spokane, Wash. | Recovered | 40 weeks; lived 3 hr.; normal, 5 lbs. 2 oz. | Hamblen, R. N.: West. J. Surg. 48: 310, 1940. |
| Sept. 12, 1938 | Hains | Bundaberg, Queensland | Recovered | Right hip was turned in; 3,200 Gm. | Hains, I. C.: M. J. Australia 1: 268, 1939. |
| March, 1939 | Cunningham | Ireland | Recovered | 36 weeks; lived; 4 lbs. 4 oz. | Cunningham, J. P.: Irish J. M. Soc., 846, 1939. |
| Mar. 18, 1939 | White and Clark | Asheville, N. C. | Recovered | 40 weeks; lived; normal | White, R. A.: North Carolina M. J. 2: 87, 1941. |
| Mar. 28, 1939 | Nicodemus | Danville, Pa. | Recovered | 38 weeks; viable; lived; female 4 lbs. 9 oz. | Nicodemus, R. E., and Carrigg, L. G.: Am. J. Obst. & Gynec. 39: 153, 1940. |
| July 18, 1939 | Maver and Marino | New Orleans, La. | Recovered | 42 weeks; lived; normal, 7 lbs. 13 oz. | Beacham, W. D., and Beacham, D. W., Obst. & Gynec. Survey 1: 777, 1946. |
| Aug. 4, 1939 | Sprague and Chappel | Athens, Ohio | Recovered | 36 weeks; lived 48 hr.; female. 7 lbs. 2 oz. | Sprague, J. R., and Chappel, M. R.: Ohio State M. J. 36: 520, 1940. (Child had asymmetrical head and equinus varus.) |
| Nov. 16, 1939 | Renner | Goodland, Kan. | Recovered | 40 weeks; normal, 6 lbs. ¾ oz. | Renner, M. J.: J. Kansas M. Soc. 42: 245, 1941. |

ANTEPARTUM HEMORRHAGE*

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THE first section of this presentation is based upon a survey of the cases of premature separation of the normally implanted placenta occurring in the Philadelphia Lying-in Hospital during the twelve-year period from 1934 to 1945. Cases presenting this complication prior to the twenty-eighth week of pregnancy have been excluded from the study.

TABLE I. INCIDENCE OF PREMATURE SEPARATION OF THE PLACENTA
Philadelphia Lying-in 1934-1945 (inclusive)

| | |
|------------------------------|----------|
| Total number of deliveries | 28,288 |
| Number of cases of abruption | 113 |
| Incidence of abruption | 1 in 250 |

The wide variation in the recorded incidence of abruption of the placenta can be accounted for by the strictness of the criteria which one establishes for the inclusion of cases. For the purpose of this study we have excluded all cases in which there was no clinical evidence of separation. An almost equal number was eliminated in which the condition was recognized only after delivery of the placenta by the discovery of small retroplacental clots, or minute organized areas of separated placental tissue. The group of 113 cases is composed, therefore, only of those presenting one or more of the following typical clinical manifestations of placental separation: continuous uterine pain, tenseness and tenderness of the uterus, evidence of intranterine hemorrhage, or frank external bleeding.

TABLE II. ETIOLOGICAL FACTORS IN PREMATURE SEPARATION

| | NUMBER | PER CENT |
|---------------------------|--------|----------|
| Toxemia of late pregnancy | 54 | 48 |
| Unknown | 59 | 52 |
| Total | 113 | 100 |

Hypertension and/or albuminuria were found in almost one-half of the entire group, and in many of those in which the etiology is recorded as unknown. rather typical symptoms such as abnormal gain in weight and edema, strongly suggested the presence of toxemia. A pre-existing hypertension in many others may have been masked by a fall in blood pressure incident to hemorrhage. A definite history of trauma was elicited in only one instance; in this patient the co-existence of toxemia was a more likely cause of the separation.

*Read by invitation before the South Atlantic Association of Obstetricians and Gynecologists February 8, 1947, at Savannah, Georgia.

A laparotomy was performed on May 13, 1947, with preoperative diagnosis of abdominal pregnancy versus uterine fibromyomas with intrauterine pregnancy. The fetal membranes were found free in the abdominal cavity. The membranes were opened and a grossly deformed living baby was found which died in thirty minutes. The placenta was attached to the uterus posteriorly between the broad ligaments, to the right iliac fossa, posterior abdominal structures, and small bowel. The cord was cut short. The placenta was left intact and the abdomen was closed without drainage.

On her sixteenth postoperative day the patient is in good condition but is still febrile.

Conclusions

Only about one-fourth of all the extrauterine pregnancies diagnosed after the fifth month of gestation will result in viable, living babies. About one-third of all these living, viable babies delivered from extrauterine pregnancies will have major or minor deformities including those which were incompatible with life. Approximately half of all the viable, living babies delivered from extrauterine pregnancies will survive eight days or more.

Summary

All the available literature on extrauterine pregnancies resulting in viable, living babies is reviewed to determine their ultimate fate.

Forty-one cases are tabulated from the literature to supplement those previously summarized.

Four new cases of extrauterine pregnancies with living, viable babies are reported from Charity Hospital of Louisiana, at New Orleans.

The authors wish to acknowledge their appreciation to Drs. Adolph Jacobs, D. W. Goldman, and E. L. King for use of cases on their services.

References

1. Beacham, W. D., and Beacham, D. W.: *Obst. & Gynec. Survey* 1: 777, 1946.
2. Hellman, A. M., and Simon, H. S.: *Am. J. Surg.* 29: 403, 1935.
3. Lelling, E.: *Zentralbl. f. Gynäk.* 62: 2209, 1938.
4. Mitra, S.: *Calcutta M. J.* 39: 1 and 43, 1942.
5. Stabler, F.: *Brit. M. J.* 1: 779, 1938.
6. Sittner: Quoted from Hellman and Simon.²
7. Winckel, V.: Quoted from Lelling.³

of the uterus close the bleeding sinuses of the placental site. If, therefore, the separation is of major degree and if the patient cannot be immediately and safely delivered by simple measures from below, we feel that cesarean section is the treatment of choice. In the more severe cases cesarean section is done in the interest of the mother, even though the child is known to be dead. Before instituting any procedure for delivery, it is imperative that the patient be treated for shock and that lost blood be adequately replaced by transfusion. A fine point of judgment is required in determining how long to postpone operative measures while awaiting reaction from shock. No arbitrary rules can be enunciated, as every case must be individually considered.

TABLE VII. MATERNAL MORTALITY FROM ABRUPTIO: 1934-1945

| | NUMBER | PER CENT |
|---|--------|----------|
| Number of cases of abruptio | 113 | |
| Number of maternal deaths from abruptio | 2 | 1.8 |

TABLE VIII. MATERNAL MORTALITY ACCORDING TO METHOD OF DELIVERY: 1934-1945

| | | |
|-----------------------------------|-----------------------|------|
| Vaginal delivery | 1 death in 47 cases | 2.1% |
| (Patient died of acute hepatitis) | | |
| Cesarean section | 1 death in 66 cases | 1.5% |
| Total maternal mortality | 2 deaths in 113 cases | 1.8% |

Removal of the uterus was deemed advisable in but four of the 66 patients who were treated by cesarean section. We do not remove the uterus simply because of its darkened appearance from extravasation of blood, but only if it fails to contract following its evacuation. There was no fatality incident to this procedure.

Following delivery, attention must be given to the likelihood of postpartum hemorrhage. Many of these uteri fail to remain firmly contracted, and a relatively small amount of bleeding will be poorly tolerated by the patient who has already suffered a considerable loss of blood. Firm packing of the uterus and vagina is urgently indicated, on the least provocation, as is also the intravenous administration of oxytocics.

TABLE IX. GROSS FETAL MORTALITY FROM ABRUPTIO: 1934-1945

| | | |
|---|-----|-----|
| Total number of cases of abruptio | 113 | |
| Total number of fetal deaths | 39 | 35% |
| Stillborn | 19 | |
| Neonatal deaths | 20 | |
| (19 of the 39 dead babies weighed less than 4 pounds) | | |
| Corrected fetal mortality | | 21% |

Since fully one-fourth of the babies were dead in utero at the time of admission to the hospital, and since nineteen of the babies weighed less than four pounds, the total uncorrected mortality rate of 35 per cent is better than had been anticipated. There is no doubt, however, that this could be substantially reduced by more prompt recognition of the significance of the symptoms on the part of both patient and physician.

The following are brief summaries of the two fatal cases of abruptio placentae.

CASE 1.—A toxic patient had profuse bleeding and signs of abruptio at the eighth month, about four hours after the onset of labor. She was delivered of a six-pound stillborn child by forceps. Free postpartum bleeding continued

TABLE III. TIME OF OCCURRENCE OF ABRUPTIO

| | CASES | PER CENT |
|--------------|-------|----------|
| Before labor | 63 | 56 |
| During labor | 50 | 44 |
| Total | 113 | 100 |

TABLE IV. SEVERITY OF CASES OF ABRUPTIO

| | |
|----------|-----|
| Mild | 35 |
| Moderate | 39 |
| Severe | 39 |
| Total | 113 |

The mild cases were those occurring, almost without exception, during labor, manifested by somewhat more than usual bleeding, some increase in uterine tension, and, occasionally, evidences of slight or moderate fetal distress. In this group there were no maternal deaths. The severe cases were those in which there was evidence of a large concealed or external hemorrhage.

TABLE V. METHOD OF DELIVERY IN ABRUPTIO; 1934-1945

| | | CASES | PER CENT |
|-----------------------|----|-------|----------|
| Vaginal Delivery | | 47 | 42 |
| Forceps | 23 | | |
| Spontaneous | 19 | | |
| Podalic version | 1 | | |
| Breech extraction | 4 | | |
| Abdominal Delivery | | 66 | 58 |
| Cesarean section | 62 | | |
| Porro cesarean | 4 | | |
| Total number of cases | | 113 | 100 |

The choice of treatment in cases of abruptio is dependent upon several factors, chief among which are the severity of the symptoms, the general condition of the patient, whether or not the patient is in labor, and, most important, the degree of cervical dilatation. In dealing with the milder degrees of separation occurring in the course of labor, in which neither the mother nor the baby present evidence of distress, it is rarely necessary to interfere with the normal course of labor. This is evidenced by the fact that of the forty-seven patients with mild or moderate degrees of separation who were delivered by forceps, breech extraction, or spontaneously, only one patient died; in this case acute hepatitis was primarily responsible for death. As seen in the following table, three-fourths of the patients whose abruptio occurred during labor were delivered vaginally.

TABLE VI. METHOD OF DELIVERY ACCORDING TO ONSET OF LABOR

| | CASES | PER CENT |
|-----------------------|-------|----------|
| Abruptio during labor | 50 | |
| Cesarean section | 12 | 24 |
| Vaginal delivery | 38 | 76 |
| Abruptio before labor | 63 | |
| Cesarean section | 54 | 86 |
| Vaginal delivery | 9 | 14 |

On the other hand, the more urgent cases, because of extreme loss of blood and shock require that the uterus be emptied by the quickest method compatible with safety to the mother. Not until the uterus is empty can firm contraction

the twenty-eighth week of pregnancy in which the diagnosis was definitely established by feeling the placenta through the cervix, its visualization by x-ray studies, or by confirming its low attachment at the time of cesarean section. By observance of these strict criteria, a large number of cases of mild painless bleeding were eliminated, even though it is quite likely that a relatively low implantation of the placenta existed in many of these cases.

TABLE XI. INCIDENCE OF PLACENTA PREVIA; PHILADELPHIA LYING-IN HOSPITAL 1934-45 (INCLUSIVE)

| | |
|------------------------------------|----------|
| Total number of deliveries | 28,288 |
| Number of cases of placenta previa | 92 |
| Incidence of placenta previa | 1 in 307 |

TABLE XII. TYPES OF PLACENTA PREVIA

| | NUMBER |
|------------|--------|
| Lateral | 25 |
| Marginal | 33 |
| Central | 20 |
| Not stated | 14 |
| Total | 92 |

As seen in the foregoing table the marginal type, in which the placenta covered only a portion of the internal os, was most frequently encountered. Next in order of frequency were lateral and central implantations.

TABLE XIII. METHODS OF DELIVERY IN PLACENTA PREVIA

| | | CASES | PER CENT |
|------------------------|---|-------|----------|
| Vaginal delivery | | 17 | 19 |
| Forceps | 5 | | |
| Spontaneous | 6 | | |
| Version and extraction | 3 | | |
| Breech extraction | 2 | | |
| Braxton-Hicks version | 1 | | |
| Cesarean section | | 75 | 81 |

The choice of treatment in placenta previa is dependent upon the following factors: the severity of hemorrhage, the degree of shock, the location of the placenta, the viability of the child, its presentation, and, most important of all, the amount of cervical dilatation.

If the bleeding occurs during labor, and the placenta is marginal or lateral, and the presentation is polar, rupture of the membranes will most often allow the presenting part to make sufficient pressure on the separated placenta to control the bleeding. In such instances we allow labor to proceed to spontaneous delivery or to a low forceps application. If the cervix is completely dilated and if the baby is small, version and extraction may occasionally be the procedure of choice, except in the central type of implantation. Because of the potent danger of deep laceration of the cervix extending into the placental site, we feel that the manual dilatation of the cervix is strictly contraindicated.

Braxton-Hicks version, while occasionally a lifesaving measure for the mother under emergency conditions, is, we believe, best reserved for those cases of marginal and lateral placenta previa in which the child is dead or not viable.

By following these principles, we were able to deliver seventeen of our patients by the vaginal route, with no maternal mortality.

despite packing of the uterus and vagina. A total of 2,250 c.c. of whole blood and infusions of glucose were given. The patient died six days after delivery, of acute hepatitis as proved at necropsy. This death was considered in staff conference as nonpreventable.

CASE 2.—An 18-year-old Negro patient, whose early prenatal course was eventful, was admitted in mild pre-eclampsia at full term. The fetal heart sounds could not be heard. Her cervix was not dilated and her pains were irregular until one hour after admission. At that time her membranes ruptured spontaneously; she had a moderate amount of external bleeding. One hour later she had definite evidence of concealed hemorrhage and cesarean section was elected. In the hour and a half elapsing before operation, her blood pressure fell from 140/90 to 80/50. Because of this, an infusion of plasma was started simultaneously with the operation. A stillborn child and the completely separated placenta, along with 2,000 c.c. of blood were evacuated from the uterus. The uterus was packed and routine closure was performed. A transfusion of 500 c.c. of whole blood was given, but the patient failed to react and died one hour after completion of the operation. This death was reviewed in staff conference and was considered to have been preventable in that shock was not adequately treated before operation and that replacement of blood loss was insufficient.

Summary

Review of this series of cases of premature separation of the placenta will, we believe, establish the following principles concerning this complication:

1. Since toxemia of pregnancy is thought to be a potent etiological factor in approximately one-half of such cases, good prenatal care offers much in the way of prevention of abruptio.
2. No patient with hypertension should be allowed to be far from expert obstetric care.
3. Early recognition by both patient and physician, of the significance of antepartum hemorrhage is imperative.
4. In a decision to delay interruption of pregnancy in toxemia patients until the time of greater viability of the child, consideration must be given to the possibility of premature separation.
5. If the case be one of mild degree, the conduct of labor may be unaltered except for increased vigilance on the part of the attendant.
6. In the more severe cases the best interests of both mother and baby are served by as prompt evacuation of the uterus as is compatible with safety.
7. Manual dilatation of the cervix and other traumatic procedures for delivery have no place in the elective treatment of abruptio.
8. Treatment for shock and replacement of blood before instituting measures for delivery will greatly decrease the operative risk.
9. Prompt replacement of blood following delivery decreases not only the immediate danger, but also lessens the incidence of puerperal infection.

Placenta Previa

The second section of this presentation consists of a study of our experience with cases of placenta previa at the Philadelphia Lying-in Hospital from 1934 to 1945. We have included in this survey only those cases occurring beyond

Our experience has resulted in our adoption of certain principles in the management of placenta previa.

1. Accurate diagnosis of the cause of bleeding is essential. A cautiously performed vaginal examination may reveal that the bleeding is due to a cervical polyp, an erosion, or, rarely, a cervical carcinoma, rather than to a placenta previa. Examination, however, entails the danger of sudden profuse bleeding as well as the risk of infection. It is our invariable rule that no patient suspected of placenta previa be examined until the operating room is ready for both vaginal and abdominal delivery.

X-ray studies by the "soft tissue" technique have in the past few years been a valuable aid in localization of the placenta. By this method the normally situated placenta is well visualized in practically all cases; the low-lying placenta is hidden by the pelvic bones. Finding the placenta high in the uterus is definite evidence against placenta previa; failure to visualize it indicates that the placenta is probably, but not necessarily, located in the lower uterine segment. The technique is, therefore, dependable only in ruling out, rather than positively diagnosing, placenta previa. This method of study is applicable obviously only to those patients whose bleeding has almost or entirely ceased. Our experience with the cystogram technique of Ude and Urner has led us to doubt its clinical value.

2. Treatment of shock and replacement of blood by transfusions of whole blood or plasma are essential before instituting procedures for delivery. Indeed, the patient should not be examined until she has reacted, because of the danger of additional hemorrhage from digital dislodgement of the placenta.

3. Expectant treatment of patients with placenta previa in the hope of bringing the child to greater viability is never justified unless the patient remains in the hospital throughout the remainder of pregnancy.

4. The method of delivery is almost wholly dependent on the status of the cervix. Because of the danger of profuse hemorrhage from the vessels of the placental site and the added risk of infection, manual dilatation of the cervix and forcible vaginal delivery have no place in the treatment of this condition. If the cervix is dilated and the placenta previa is only partial or marginal, rupture of the membranes will allow the presenting part to make pressure on the placenta sufficient to stop the hemorrhage. Under similar conditions version and extraction are indicated only if the cervix is *completely* dilated. Braxton-Hicks version, we feel, should be utilized only in those cases in which the baby is dead or nonviable and in which the cervix is partially dilated. While it is undoubtedly a valuable means of saving maternal life under emergency conditions, it entails almost certain sacrifice of the child.

The hydrostatic bag possibly has its place in the treatment of certain cases of marginal and lateral placenta previa but several instances of continuing intrauterine hemorrhage following its insertion have resulted in our abandonment of this procedure:

In all cases in which the cervix is not dilated, in all cases of central placenta previa regardless of the cervical dilatation, and in those of malpresentation

In seventy-five of our cases, cesarean section was performed. If the bleeding is profuse and the cervix is closed, we feel that the interests of both mother and child are best served by this procedure. Regardless of the amount of cervical dilatation cesarean section is done in practically every case of central placenta previa and in most instances of malpresentation.

TABLE XIV. MATERNAL MORTALITY FROM PLACENTA PREVIA; 1934-1945

| | | |
|--|----|--------|
| Number of cases of placenta previa | 92 | |
| Number of maternal deaths from placenta previa | 2 | (2.2%) |

TABLE XV. MATERNAL MORTALITY ACCORDING TO METHOD OF DELIVERY; 1934-1945
(PLACENTA PREVIA)

| | | PER CENT OF MORTALITY |
|--------------------------|----------------------|--------------------------|
| Vaginal delivery | 0 deaths in 17 cases | 0.0 |
| Cesarean section | 2 deaths in 75 cases | 2.7 |
| Total maternal mortality | 2 deaths in 92 cases | 2.2 |

As seen in the above table, there were no deaths among the seventeen patients in whom the amount of cervical dilatation and other favorable factors permitted vaginal delivery. Unfortunately, a relatively small number were found amenable to such simple measures.

Following are the summaries of the two fatal cases of placenta previa:

CASE 1.—Cesarean section was done for central placenta previa under gas, oxygen, ether anesthesia. Bleeding was not profuse. The patient was obese (232 pounds), and was not in shock. She died of bronchopneumonia on the fifth postoperative day. The baby lived. This death was considered nonpreventable in our staff conference.

CASE 2.—The patient, with history of slight painless bleeding for six weeks, had a medical induction of labor, including three minims of pitocin. She immediately began to bleed steadily but not profusely. Cesarean section was done because of marginal placenta previa with only two fingers dilatation of the cervix. Profuse hemorrhage occurred during anesthesia. The baby lived. The mother failed to react to infusion during, and transfusion after operation. She died of shock and hemorrhage one and one-half hours later. This case was considered preventable in our staff conference in that shock was not adequately treated, a sufficient amount of blood was not given, and pitocin was used in the induction of labor.

TABLE XVI. GROSS FETAL MORTALITY ACCORDING TO METHOD OF DELIVERY
(PLACENTA PREVIA)

| | | PER CENT OF MORTALITY |
|---|-----------------------|--------------------------|
| Vaginal delivery | 9 deaths in 17 cases | 53 |
| Cesarean section | 15 deaths in 75 cases | 20 |
| Total fetal mortality | 24 deaths in 92 cases | 26 |
| (Nine of the 24 dead babies weighed under 4 pounds) | | |
| Corrected fetal mortality | | 18.5 |

Intrauterine asphyxia was presumably responsible for eleven fetal deaths and was, no doubt, a contributory cause in all of them. Prematurity was the next most frequent factor, as nine of the twenty-four babies who died weighed less than 4 pounds.

THE ELECTIVE USE OF KIELLAND FORCEPS IN MANAGEMENT OF OCCIPITOPOSTERIOR AND OCCIPITOTRANSVERSE POSITIONS

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MANAGEMENT of labor in occipitoposterior and transverse positions of the fetal head has been in a static stage for many decades. The utmost of conservatism still prevails in the teaching and in the literature dealing with this subject. Whether the writer favors manual rotation to an anterior position with subsequent delivery with conventional forceps as advocated by Danforth¹⁻²; rotation of the head by "key in lock" multiple application of forceps; or some modification of the Seanzoni maneuver (Danforth³); or the use of Barton forceps (Langman and Taylor⁴); or the Kielland forceps (Kushner and Wahrsinger⁵); all agree that before any attempt to terminate labor full dilatation of the cervix with strong labor pains should have occurred for two hours or more, or that there shall be obvious signs of either fetal or maternal distress or both.

In this presentation I offer a critical analysis of 2,601 consecutive deliveries of private patients in which Kielland forceps were used in 547 instances of occipitoposterior and transverse positions. In the great majority of these 547 instances the forceps were used as an elective procedure to rotate and deliver the fetal head as soon as, or shortly after, full dilatation was obtained.

Occipitoposterior and transverse positions of the fetal head occur frequently, according to Bacon,⁹ 30 per cent of all vertex presentations; Danforth,¹⁻² 26 per cent; and Calkins,²¹ 48.3 per cent. Spontaneous rotation to an anterior position does occur frequently depending on a number of factors, the size of the fetal head and the size of the pelvis, the length of time allowed for molding of the head, the strength of the forces of labor and the internal contour of the pelvic passage. Much light has been shed on this last factor by the work of Caldwell and Moloy⁶ and Caldwell, Moloy, and D'Esopo⁷⁻⁸ in describing by means of extensive x-ray studies the type of pelvis in which posterior and transverse positions are likely to persist.

Kielland Forceps

American medical literature is not replete with articles pertaining to the use of Kielland forceps. Although Kielland presented his forceps and described in detail his method of using the instruments in 1915, it was not until 1924 that Greenhill¹⁰ made a thorough study of collected reports from European literature. Since then sporadic articles have appeared in American medical journals.¹¹⁻¹⁹ Most of these articles are brief accounts of the use of Kielland forceps in a small series of cases. Kushner and Wahrsinger⁵ and Langman and Taylor⁴ presented excellent statistical studies of significantly large series of cases.

Lengthy descriptions of the forceps themselves and the method of their use are not necessary. There are, however, a few points that will bear emphasis.

of the fetus, cesarean section is the safest, and therefore the most conservative form of treatment.

5. The use of an oxytocic intravenously immediately on completion of the second stage of labor, and firm packing of the uterus and the vagina after expulsion or removal of the placenta will considerably lessen the danger of postpartum hemorrhage. In most instances packing the uterus after cesarean section for placenta previa is advisable.

6. Blood transfusions are indicated following delivery to combat anemia and to improve the patient's resistance to infection.

Summary

1. A series of 113 cases of premature separation of the placenta is reported, with a maternal mortality rate of 1.8 per cent.

2. A series of 92 cases of placenta previa is reported, with a maternal mortality rate of 2.2 per cent.

3. Methods of management of these two complications are discussed.

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of the forceps. Too early elevation of the handles causes deflexion of the head with the result that too great force is necessary to bring about delivery and the more unfavorable diameter of the head as it is forced through the birth canal may result in severe lacerations of the outlet.

Material

The material for this analysis consists of 2,588 consecutive private patients delivered at St. Joseph's Hospital and at the Southwestern Presbyterian Hospital. Neither of these hospitals has an intern or resident staff. Labors and deliveries were conducted by myself with the assistance of a very efficient nursing staff. In order to have the results uniform and not subject to personal variation, the work of my associates is not included in this report. With necessary variations to suit individual cases, a definite routine as regards nutrition, elimination, observation and medication was carried out in all cases. All labors were conducted by vaginal examinations preceded in each instance by a vaginal instillation of 15 c.c. of a 5 per cent aqueous solution of Mercurochrome. In this series 2,588 mothers were delivered of 2,601 babies, twins having occurred twenty-six times. Table I shows the distribution of these cases by presentation of the fetus.

TABLE I

| PRESENTING PART | NUMBER | PER CENT |
|-----------------|--------|----------|
| Vertex | 2,499 | 96.07 |
| Breech | 93 | 3.60 |
| Shoulder | 7 | .26 |
| Face | 2 | .07 |
| Total | 2,601 | 100.00 |

Table II breaks down these figures still further to show the method of delivery.

TABLE II

| TYPE OF DELIVERY | NUMBER | PER CENT |
|--|--------|----------|
| Breech | 93 | 3.60 |
| Version and extraction | 26 | 1.00 |
| Cesarean section | 78 | 2.99 |
| Decapitation | 1 | .038 |
| Craniotomy (hydrocephalus) | 1 | .038 |
| Occipitoanterior (spontaneous or outlet forceps) | 1,808 | 69.51 |
| Occipitoposterior (Scanzoni or key in lock) | 7 | .26 |
| Occipitoposterior (manual rotation) | 9 | .346 |
| Occipitoposterior (delivered as such) | 31 | 1.19 |
| Occipitoposterior (Kielland forceps rotation) | 547 | 21.03 |
| Total | 2,601 | 100.00 |

These 547 cases in which Kielland forceps were used for rotation and delivery of fetuses presenting in occipitoposterior position were comprised of two groups of patients. Thirty-six of these patients were referred to me for delivery after attempts at delivery, including attempts at forceps delivery, version and full doses of pituitrin, had failed. Some of these women had traveled long distances, one came over 200 miles. These women all presented the classical findings referred to as the customary indications for operative intervention. These

With two exceptions, the instruments should always be applied in the original Kielland manner. This consists in first introducing the anterior blade well into the uterine cavity, and then rotating it into apposition with the fetal head. This rotation should cause the tip of the blade to describe an arc in a "clockwise" direction when the occiput is directed to the right side of the mother's pelvis, and "counter clockwise" when left occipitoposterior or transverse position of the head is present. In actual use two fingers of the left hand are inserted into the vagina and between the cervix and the fetal head. The head should not be disengaged or disturbed in any manner. The tip of the anterior blade, pointing upward, is then inserted between the fingers in the vagina and the cervix. Frequently as the blade passes into the uterine cavity there is encountered a definite resistance. If the examining fingers are thrust upward this resistance is found to be due to a constriction of the uterine muscle at the level of the junction of the cervix with the uterine musculature. Johnson²⁰ has described this condition and calls it "temporary or functional contraction ring." If delivery is too long delayed, this "functional" contraction ring may become the pathologic contraction ring. When this resistance is encountered the handle of the forceps is elevated and the tip of the blade passes readily into the uterine cavity, where it can be rotated and applied to the fetal head. The posterior blade is then inserted and articulated with the anterior blade.

The two exceptions to this method of insertion of the blade are: first, when a true contraction ring is present it is dangerous to attempt the insertion of the blades by the rotation method and in this case the "wandering" manner of insertion is advisable; second, when the head is low in the pelvis and the occiput is directly posterior the blades are applied to the sides of the fetal head exactly as with classical forceps, keeping the markers on the handles directed toward the occiput. The head may then be rotated without difficulty and delivered with a single application of the forceps.

Rotation of the head may be accomplished by one of three procedures:

1. *Rotation without traction.* If the head is lying in the plane of greatest pelvic diameter, gentle rotation of the handles in a straight line and not with a sweeping movement, will usually suffice to bring the occiput to an anterior position.

2. *Rotation with traction.* If the method described above does not readily produce rotation, traction with rotation simultaneously applied will produce rotation accompanied by descent of the head.

3. *Disengagement of the head with rotation above the pelvic brim.* This would appear to be a dangerous and radical procedure. However, the cephalic curve of Kielland forceps fits the fetal head so accurately that thrusting the head up and out of the pelvis does disengage the head from the forceps. The head is readily rotated to an obliquely anterior position and traction with the resulting descent of the head and further rotation brings the head to the desired anterior position and delivery is effected.

It is, of course, understood that there is no cephalopelvic disproportion existing that precludes the possibility of delivery through the vagina. Traction for delivery should be applied in the direction naturally taken by the handles

ered by Kielland forceps than in the other group was laceration involving the rectum, five cases in the Kielland forceps group, and two cases in the mothers delivered by other means. In only one instance did the laceration include the sphincter muscle, the others were lacerations into the lumen of the bowel above the sphincter muscle. All were treated by immediate repair and all healed without complication. The one complete tear followed use of conventional forceps. On discharge from the hospital, and at the postpartum examination, her sphincter control was good.

From the above analysis it is evident that, as far as the mother is concerned, there is no appreciable difference in the outcome of delivery as the result of the elective use of Kielland forceps as compared with the other methods of delivery.

Fetal End Results

The object of all obstetric care is to complete the cycle of pregnancy, parturition, and puerperium with a well mother and a well baby. Table IV analyzes the results from the standpoint of fetal survival.

TABLE IV

| | | |
|---|-------|-------|
| Total births other than by Kielland forceps | 2,054 | |
| Stillbirths under 1,500 Gm. | 10 | 0.48% |
| Stillbirths over 1,500 Gm. | 33 | 1.6 % |
| Neonatal deaths under 1,500 Gm. | 22 | 1.07% |
| Neonatal deaths over 1,500 Gm. | 16 | 0.78% |
| Total births by Kielland forceps | 517 | |
| Stillbirths over 1,500 Gm. | 5 | 0.9 % |
| Neonatal deaths over 1,500 Gm. | 8 | 1.46% |

Among the babies delivered by Kielland forceps there were no fetuses under 1,500 Gm. in weight. Of the five stillborn fetuses, four were badly macerated at birth. Of the eight neonatal deaths among the fetuses delivered by Kielland forceps, autopsy demonstrated three cases of anatomical conditions incompatible with life: pulmonary atelectasis one, congenital cystic kidney one, hydrocephalus and spina bifida one. Excluding these three cases of congenital deformity, the corrected neonatal mortality is 0.90 per cent. Of the five remaining neonatal deaths only one autopsy was obtained, and that showed the cause of death to be intracranial hemorrhage, and the same cause was ascribed to the other four deaths. These deaths occurred in the group of cases that would be usually classified as "indicated" Kielland forceps deliveries. In the group of fetuses delivered by the "elective" use of Kielland forceps such fetal complications as marked molding of the fetal head, caput succedaneum and cephalhematoma were almost entirely absent.

There were only six instances in which delivery could not be effected by Kielland forceps. In these six cases the forceps were successfully applied and rotation was accomplished, but traction did not result in descent of the head and the forceps were removed. Cesarean section was performed twice with good results to mother and baby, version was done four times, with good result in three. In the fourth case, not considered as safe to perform a section, the version delivery resulted in fetal injury which developed into hydrocephalus of traumatic origin and the child died at the age of 2 years.

Discussion

It is now a matter of general agreement that, as far as the mother is concerned, the skillful use of forceps under suitable conditions to effect delivery, does not affect the outcome so far as life and health are concerned. From the

patients had all been in labor for hours without progress, the mothers were in a state of near exhaustion, the fetal heads were all extremely molded, and the fetuses were all in evident distress if not already dead. This group contributed largely to the number of morbid mothers and to stillborn infants and to neonatal deaths.

The remaining 511 cases consisted of mothers who were under my care from early in pregnancy through labor. In this group of patients I did not set any arbitrary time limit before which operative assistance* was contraindicated, such as two or more hours of hard second stage labor, nor did I wait for signs of maternal or fetal distress or both. When the cervix was fully dilated and the head deeply engaged in the pelvis, the patient was taken to the delivery room and prepared for delivery. Under anesthesia the Kielland forceps were applied in the original manner and the head rotated and delivery effected. I do not consider it to be necessary or advisable to remove the Kielland forceps and apply conventional instruments for the actual delivery.

Maternal End Results

Such a radical departure from the conventional indications for any procedure to assist rotation and delivery of the fetus presenting in occipitoposterior or occipitotransverse positions must be justified by the results obtained. The results are presented in Table III, showing the effect of the procedure from the maternal standpoint. The standard of morbidity used in this series is that established by the American College of Surgeons. There were no deaths from infection in the entire series. Of the patients delivered by Kielland forceps who had a febrile puerperium, seven were among those patients who were brought to the hospital after long labor and attempts at delivery made at home under anything but proper conditions. All seven had intrapartum infection before arrival at the hospital.

TABLE III

| | | |
|--|-------|-------|
| Total mothers delivered | 2,588 | |
| Total morbidity | 95 | 3.67% |
| Mothers delivered other than by Kielland forceps | 2,041 | |
| Morbidity | 76 | 3.72% |
| Mothers delivered by Kielland forceps | 547 | |
| Morbidity | 19 | 3.47% |

Actual causes of morbidity of the entire group were as follows: acute pyelocystitis, thirteen; acute respiratory tract infection, five; active pulmonary tuberculosis, two. All the remaining febrile reactions were considered to be puerperal in origin. There were three cases of thrombophlebitis in the entire series. *No prophylactic administration of sulfonamides or penicillin was used.* These drugs were administered on indication only and the sulfonamides were used in exactly fifty instances, and penicillin in only six cases. Total maternity mortality in the 2,588 mothers was six. In the series of 547 mothers delivered by Kielland forceps there were two deaths, neither death could be attributed to the method of delivery. One death occurred in the case of an eclamptic woman who was brought to the hospital comatose and moribund, and the other death was due to a pulmonary embolus.

Other maternal complications in this series were postpartum hemorrhage and lacerations or extensions of episiotomy incisions involving the rectum. Postpartum hemorrhage occurred in the group of 547 women delivered by Kielland forceps in six cases, or 1.09 per cent, and among the 2,041 women delivered by other means the occurrence of hemorrhage was twenty-two, or 1.07 per cent. The only complication that occurred with greater frequency in those mothers deliv-

*The terms "operative interference" and "operative intervention" should be deleted from obstetric terminology and the term "operative assistance" substituted.

2. Maternal morbidity and maternal complications were not increased by the procedure of early application of Kielland forceps.

3. Two maternal deaths occurred in this series of 547 deliveries, neither of which could be attributed to the method employed in delivery.

4. The total fetal loss was thirteen—net loss ten.

5. The best results from the fetal standpoint were in those instances in which Kielland forceps were applied early in the second stage of labor.

6. The early application of Kielland forceps is accomplished with less difficulty and with much less occurrence of damage to either mother or baby than the application late in the second stage of labor.

7. Kielland forceps are ideal for dealing with occipitoposterior and transverse positions.

8. The use of Kielland forceps under suitable conditions as an elective procedure is recommended in dealing with these cases.

My appreciation is tendered to Sister Williamama, Medical Librarian of St. Joseph's Hospital, and to Miss Lillian Henningson, Medical Librarian of the Southwestern Presbyterian Hospital, for their assistance in making these records available for study.

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maternal viewpoint, the end result of the use of forceps is that labor is shortened. In spite of a great variety of procedures aimed at decreasing the pain of childbirth, ranging from mental suggestion to continuous caudal anesthesia; in spite of a great variety of analgesic drugs, the fact remains that the *one positive thing* we can do to lessen the pain and shorten the period of suffering is to give the parturient woman the benefit of operative assistance in delivery. Is this worth while? The late Dr. Joseph B. DeLee thought it was when he advocated the routine use of forceps in the procedure for which he coined the name *Prophylactic Forceps*.

In the case of occipitoposterior positions, it is well recognized that the first stage of labor is prolonged. Not only is the first stage prolonged, but the particular character of the pains is more severe than in occipitoanterior positions. This is probably due to the fact that in most occipitoposterior positions, the cervix lies far posterior in the hollow of the sacrum and the uneven pressure on the cervix is peculiarly painful. I have shown in this series of cases in which Kielland forceps were used early in the second stage, that the procedure is devoid of danger to the mother. Kushner and Wahrsinger⁵ state, "There were six cases of mitral stenosis, where the second stage was entirely eliminated. Forceps (Kielland) were applied when full dilatation was attained." If, as I have demonstrated in my study of 547 cases of the use of Kielland forceps, and as the writers quoted above admit, the early application of Kielland forceps in occipitoposterior and transverse positions is safe for the mother, and results in shortening her labor and relief of pain, it is therefore a worth-while procedure.

From the standpoint of the fetus which has had the misfortune to present itself in an occipitoposterior position, the matter of early versus late application of Kielland forceps with rotation and delivery is a matter of vital importance. Langman and Taylor⁴ report 134 instances of their use of Kielland forceps with fetal and neonatal loss of twenty-one. Kushner and Wahrsinger⁵ report 200 cases with a fetal and neonatal loss of fourteen. In my series of 547 deliveries with Kielland forceps, the fetal and neonatal loss was thirteen. It is not my purpose to compare my skill in the art of Kielland forceps application with these other writers. It is my intention to point out that the essential difference in results is directly due to early delivery before damage has been done to the fetus as the direct result of the forces of labor. In none of my cases was an arbitrary "watching and waiting" time required. In the great majority of my own cases, forceps were applied shortly after full dilatation was attained. The disastrous results to the fetus in my series were due to delay. It is my firm conviction that had delivery been effected earlier in labor in all instances, the fetal loss would have approached zero.

Summary and Conclusions

1. A critical study of 547 deliveries with Kielland forceps out of a total of 2,601 consecutive deliveries is presented.

use of more than one sulfonamide is found in Lehr's¹² studies of inhibition of deng precipitation in the urinary tract by sulfonamide mixtures. It was possible to obtain such a mixture of sulfa derivatives whose optimal pK_a 's and parallel pH 's would fall within the maximal and minimal pH range encountered during the course of healing of cervicovaginal operative lesions. This hypothesis was subjected to a carefully controlled laboratory study prior to initiation of the present clinical study.

The enhancement of sulfonamide activity by urea and related compounds has been demonstrated by several investigators.¹⁶⁻²⁰ This action depends on the facts that (a) bacteria, especially Gram-negative organisms, are killed or inhibited by urethane and carbamates themselves; (b) urethanes and their derivatives have a competitive action on para-aminobenzoic acid which is inhibitory to sulfonamides.

The problem of application of these drugs to the surgical area was considered. In view of the wide but convoluted epithelium of the vaginal rugae to be covered, as well as the irregular crevices and interstices occasioned by operative procedure, it was necessary to select a base which would adhere to the mucosal surfaces as well as be water-dispersible and absorptive in nature.²¹ The dosages of sulfa derivatives was determined upon a molecular equivalent basis that no more than 10 per cent of the formula were sulfa crystals by weight. This percentage of the actual principles was distributed as follows: 3.42 per cent sulfathiazole, 2.86 per cent acetyl-sulfanilamide, 3.70 per cent benzoyl-sulfanilamide and 1 per cent urea peroxide.⁶ Animal studies revealed non-toxicity and no untoward side effects. Absorption rates through intact and disrupted mucosal surfaces were performed. Rabbits weighing approximately 4.0 kg. were used in the study. Three grams of cream were applied over a shaved area upon the dorsum. Hourly blood levels were determined. The peak of absorption, at the fourth hour, was 2.50 mg. per cent in the median instance. The value never exceeded 4.0 mg. per cent in any case. Absorption of the topically applied multiple sulfa cream was rapid, reaching a peak within four hours and disappearing almost entirely from the blood within twenty-four hours. The blood concentration of the total sulfonamides was below usual sulfonamide values, rising to less than 3 mg. per 100 c.c. of whole blood at any time.

Blood levels in rabbits were determined similarly after vaginal application of 3.0 Gm. of cream. The peak blood level, at five hours, was found to be 1.87 mg. per cent or 0.35 per cent per kg. body weight. The first 25 humans in this series whose blood sulfa concentrations were determined yielded only traces, several determinations rising between 0.2 to 0.4 mg. per cent. It was obvious, therefore, that the preponderant sulfonamide activity was available to the mucosal surfaces in immediate contact.

Controlled tissue tolerance tests were carried out on albino female rats. The animals were sacrificed at varying times and histologic sections of the vagina, cervix, kidneys, and liver revealed no abnormal changes. Allergic and

*The multiple sulfa cream used in this study was the Triple Sulfa Cream prepared and furnished by the Ortho Research Foundation, Raritan, New Jersey.

A MULTIPLE SULFONAMIDE THERAPEUTIC MEASURE IN THE POSTOPERATIVE CARE OF THE CERVIX AND VAGINA*

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IN RECENT years the knowledge of vaginal physiology¹⁻⁹ has increased tremendously. In diseased states of these organs we attempt to redirect pathologic variables to a state of normal physiologic function, with judicious expedition, through the utilization of chemotherapeutic principles. Medicine's recent advances in chemotherapy have been remarkable. With these newly applied principles, the healing times in vaginal and cervical operations can be decreased considerably.

In postoperative vaginal and cervical conditions there exist four main physiologic imbalances tending to delay prompt healing:

1. The patient's vaginal flora changes, from Grade 1 to Grades 2 and/or Grade 3.

2. The pH approaches neutrality.¹⁰⁻¹³ There is a progressive swing of the pH toward that favoring the more optimal growth of secondary bacterial invaders.

3. The epithelial strata are destroyed or decreased in height. This is related to catabolic excretions of low grade pathogenic bacteria hostile to superficial mucosal cells by virtue of exotoxins and other unfavorable excretory substrates.

4. The glycogen availability of the tissue is decreased. As the upper mucosal layers, containing the greater amount of this polysaccharide, are destroyed the glycolytic needs of the secondary bacterial invaders become more adequate. A vicious circle is thus developed. Too, we are aware the acidosis of anesthetics exert a direct glycogenolytic influence upon the body tissues.²⁴ All these depriving variables contribute to the continuing depletion of normal glycogen content.

One logical approach to decrease the vaginal discharge and restore normal physiological mucosal balance was to suppress the secondary bacterial invaders. It is principally these saprophytic invaders which are responsible for the changes in the delicate physiologic equalization.

The role of the sulfonamide derivatives was considered to represent one possible approach toward the assistance of the normal reparative process, provided the formulation of such therapy considered such additional requisites to tissue repair than only the control of bacterial invaders. It is known that sulfonamide derivatives control secondary bacterial invaders at optimally specific bacteriostatic ranges. Cowles¹⁴ demonstrated that the maximal bacteriostatic action for a given sulfonamide half dissociation constant was obtained within its paralleling specific pH range. A further indication for the

*Presented before the Philadelphia Obstetrical Society, Jan. 3, 1946.

organism and stirred with a sterile glass mixer for two minutes. Subcultures were then made into thioglycollate medium containing the three above-mentioned concentrations of P.A.B.A. at five, ten, fifteen, thirty, and sixty minutes, and twenty-four hours. The subcultures were incubated for seven days. Gram-stained smears were prepared from the tubes at the critical exposure times, to make certain that the bacteria found were those used in the inoculum. All negative subcultures were again subcultured into thioglycollate broth and observed an additional seven days. All tests were run in duplicate. Two types of controls were set up: (a) the test organisms were inoculated directly into media containing three concentrations of P.A.B.A.; (b) the multiple sulfa cream direct from tubes was inoculated in the same medium in order to further check its original sterility.

The results of these tests are shown in the following table:

TABLE I. THE ANTISEPTIC ACTION OF A MULTIPLE SULFA CREAM

| TEST ORGANISM | KILLING TIME |
|--|--------------|
| <i>Bacillus anthracis</i> | 5 min. |
| <i>Pseudomonas aeruginosa</i> | 5 min. |
| <i>Bacillus subtilis</i> | 5 min. |
| <i>Streptococcus vaginalis</i> (hemolytic) | 5 min. |
| <i>Staphylococcus aureus</i> | 30 min. |
| <i>Escherichia coli</i> | 60 min. |
| <i>Clostridium perfringens</i> | 30-60 min. |
| <i>Clostridium tetani</i> | 60 min. |
| <i>Streptococcus hemolyticus, A</i> | 1-18 hr. |
| <i>Streptococcus hemolyticus, D</i> | 1-18 hr. |

All control cultures gave luxuriant growth. No evidence of bacterial growth was observed in tubes receiving the cream alone.

It was concluded that the cream destroys a wide variety of pathogenic organisms of the types commonly found in surgical wounds. The killing time in all cases was brief enough to insure the destruction of these organisms during the period of time in which a special sulfa cream would be expected to remain on the wound site.

With this experimental background, and a working hypothesis of goals we hoped to attain physiologically and therapeutically, we initiated clinical evaluations on postoperative patients in whom the mucosal continuity of some area of the lower genital tract had been broken. Our previous experience with such cases was that for a period of five to six weeks following conization, vaginal hysterectomy, and vaginal plastic operations there existed vaginal discharge, greenish-brown to yellowish-green in color, malodorous in some, and moderately profuse in amount. Upon inspection of the operative sites, particularly those involving the cervix uteri, a gray-green membrane covered the areas, appearing about the fourth day and loosening on the sixteenth to the twentieth day. This membrane was unaltered by the local application of the usual aqueous or alcoholic antiseptics, even though hydrogen peroxide had been used as a prior cleansing agent. When these factors were considered, i.e., the prolongation of healing time, localization of a slough, and the annoying discomfort and embarrassment to the patient requiring added necessity for frequent douches, the multiple sulfa cream preparation was tried. Two hundred cases were studied including 121 conizations of the cervix and 79 vaginal plastic operations.

Discussion

Within twenty-four hours after operation, or upon the removal of vaginal packs or cervical wicks, approximately 5.0 Gm. of multiple sulfa cream was

sensitization sulfonamide studies were determined by testing twenty-three human subjects with patch tests. No sensitivity was observed in any instance, again indicating major sulfa activity at site of application rather than systemic in action.

In Vitro Bacteriology Evaluations

Baeteriologic tests in vitro were then carried out, using the agar eup procedure. Two-tenths of a cubic centimeter of an eighteen-hour broth culture of *Staphylococcus aureus* was inoculated into approximately 20 c.c. of heart infusion agar adjusted to pH 4.6, 5.2 and 7.0. The multiple sulfa cream preparation was enelosed in a glass ring of 1.5 cm. in diameter and placed on top of the solidified inoculated agar. The plates were then incubated for twenty-four hours at 37° C. The zone of inhibited growth was measured in mm. as follows:

at pH 4.6 —11 mm. zone
pH 5.2 —11 mm. zone
pH 7.04—12 mm. zone

The results obtained in these experiments, as a whole, exhibited consistently clear-cut zones of bacteriostasis at the specific pH levels.

In view of our desire to evaluate multiple active sulfonamide principles upon postoperative sites, it was deemed advisable to determine the sterility of the preparation itself. The following method was used: one-tenth gram samples were taken aseptically from a portion of a tube near the orifice and again at a point approximately halfway down the tube. These amounts of the sulfa cream were placed in duplicate tubes of thioglycollate culture medium containing three different amounts of para-aminobenzoic acid. The amounts of P.A.B.A. were so adjusted in the three series that the ratio of sulfonamide to P.A.B.A. were 10/1, 100/1, 1000/1. The thioglycollate medium provided optimal culture conditions for both aerobes and anaerobes. After seventy-two hours incubation at 37° C. subcultures were made into homologous thioglycollate medium containing the same amounts of P.A.B.A. After a second incubation period of seventy-two hours, the subcultures were observed for evidence of gross bacterial populations, and the clear tubes were recorded as containing no live bacteria. All negative tubes were incubated nine days before final judgment was made. These negative tubes were then inoculated with *Candida albicans* and *Clostridium sporogenes* to determine whether or not either a pathogenic fungus or an anaerobe, if present in the original multiple sulfa cream, would have grown in the test culture medium. In addition, at the time the original test was set up, control tubes of thioglycollate medium containing the same amounts of P.A.B.A. were inoculated also with *Staphylococcus aureus*.

Duplicate samples from eight different batches of cream were tested. None were found to contain live bacteria or spores detectable by the method described above. All control tubes developed high bacterial populations and all of the negative tubes which were inoculated with *Candida albicans* and *Clostridium sporogenes* likewise supported good bacterial and fungus growth, demonstrating the validity of the test method. It was therefore concluded that the multiply-derived sulfa cream was sterile as prepared pharmaceutically.

The antiseptic action of the cream was investigated in order to gain information regarding its in vitro action against a variety of organisms which might be encountered in wound infections. The following bacteria were used: *Bacillus anthracis*, *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus vaginalis*, *Streptococcus hemolyticus*, Group A; *Streptococcus hemolyticus*, Group D; *Escherichia coli*, *Clostridium tetani*, *Clostridium perfringens* and *Pseudomonas aeruginosa*. One cubic centimeter of the specially developed sulfa cream was seeded with 0.1 c.c. of a twenty-four or forty-eight hour culture of the test

In the sixty-four vaginal plastic cases the same rapid healing time and decrease in discharge was noted. However, where complete epithelialization occurred earlier, the sutures remained in place even after thirty days, and in many cases the twenty-day catgut had to be removed much as any nonabsorbable suture material.

In these simple vaginal plastic procedures not involving cervical surgery, there was seldom any abnormal increase in vaginal discharge noted. In this group of cases the compound sulfa cream was used solely to decrease the bacterial flora. Of particular interest were two LeFort colpocleisis operations, done on women both past 70 years of age. In both instances the healing was prompt and complete. Needless to say, meticulous care was exercised in the introduction of the multiple sulfa cream along the lateral troughs.

Summary

In an attempt to enhance healing and obtain a corollary decrease in the postoperative vaginal discharges, a newly developed multiple sulfa cream was evaluated. Its component sulfonamides included sulfathiazole, N-acetyl-sulfanilamide, N-benzoyl-sulfanilamide in addition to urea peroxide. The three sulfa compounds were found useful in combatting the secondary bacterial invaders which grow more luxuriantly at the elevated and optimally pathogenic pH levels. The urea peroxide proved useful in improving the bacteriostatic and bacteriocidal action of the sulfonamide preparation itself. Urea peroxide is also bacteriocidal and does exert some debriding action upon the denuded mucosal surfaces.

Bacteriologic and histologic studies in vivo and in vitro were carried out to insure low toxicity of such topically applied multiple sulfa derivatives incorporated in an absorptive cream base.

Two hundred surgical patients have been carefully followed over a period of eighteen months and the clinical efficacy of the preparation was demonstrated.

Conclusions

1. A recently developed compound sulfa cream, embodying normal physiologic and chemotherapeutic principles, was studied and its efficacy in treating the postoperative cervix and vagina was demonstrated in 200 gynecologic cases.

2. The high bacteriostatic and bacteriocidal action of this multiple sulfa topical preparation, at the important pH ranges of 4.6, 5.2, and 7.0 was demonstrated clinically and in the laboratory. As the reparative processes of lower genital tract mucosa increased the elevated pH of the surface infected wounds regressed to normal hydrogen ion values ranging between pH of 4.0 to 5.0.

3. The compound sulfa cream is a sound addition to the postoperative period not only because of ease of administration and the fact that annoying vaginal discharges were decreased to a minimum but primarily because the healing time of such mucosal surfaces was reduced to 50 per cent of what it was previously as compared to control cases.

The author is indebted to Dr. Camille J. Stamm for his kindness in contributing his cases to this study; and to the Ortho Research Foundation for making available full experimental laboratory data.

inserted into the vaginal canal twice daily. The patients were examined twice weekly following the seventh postoperative day. At the time of each office visit the patients were questioned as to the odor, number of napkins used to control leucorrheal discharge, and localized pelvic discomfort.

One of the most annoying symptoms, the malodorous discharge, was found nonexistent in all the treated cases. On speculum inspection, the operative site was red and appeared always as a clean granulating surface without a superficial membrane attached, and no apparent slough present.

It was noted in the conization series that at the tenth and eleventh days, epithelialization was in active progress as evidenced by the furred appearance at the advancing reparative edges of the vaginal portions of the coned canal. Healing was completed as early as the sixteenth postoperative day and as late as the twenty-fourth postoperative day in contrast to twenty-eight days²² to forty-two days.²³ See Table II illustrating these time factors.

TABLE II. OPERATIVE PROCEDURES.* TWO HUNDRED CASES TREATED WITH COMPOUND SULFA CREAM IN THE POSTOPERATIVE PERIOD

| | NO. OF CASES | AVERAGE TIME OF HEALING |
|--------------------------|--------------|----------------------------|
| Anterior colporrhaphy | 29 | 16 days |
| Perineorrhaphy | 25 | 17 days |
| Colpocleisis | 2 | 17 days |
| Cervical amputation | 6 | 22 days |
| Third degree tear repair | 2 | 11 days |
| Vaginal hysterectomy | 15 | 18 days |
| Cervical conizations | 121 | 20 days |
| | <hr/> 200 | |

*Several types of lower canal surgical procedures were performed upon single cases.

In 899 conization cases Miller and Todd²³ found an incidence of proved stenosis in 6.46 per cent with a probable incidence in an additional 2.51 per cent. In our series the cervical canals were sounded upon the 21st day in all conization cases and no occlusions were discovered. There was, however, a slight increase in the amount of granulation ooze noted during the second postoperative week, as compared to the amount seen previously in patients where slough was present in those who had not been treated with the multiple sulfa cream in the postoperative period. Before this treatment was instituted we noted an increase in the amount of bleeding at about the twenty-fifth day, which was then attributed to the detachment of the sloughing membrane covering the thrombosed and infarcted vessels. Since the same bleeding takes place with multiple sulfa therapy during the second postoperative week, and since this stage corresponds to the twenty-fifth day or thereabouts in the healing schedule without therapy, it may be the ooze is occasioned by the beginning of the epithelialization and onset of angiomatous proliferation. Histologic work on this subject is now in progress.

In this series of cases one patient developed a parametrial abscess which necessitated posterior colpotomy. The operative vaginal site, however, showed rapid healing. Following evacuation of the parametrial abscess, complete recovery ensued.

ANEMIAS OF PREGNANCY

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A DECREASE in the hemoglobin concentration, hematocrit, and erythrocyte count of the peripheral blood occurs during pregnancy. True anemia of pregnancy has been defined as a condition in which these constituents are reduced below the level considered physiologic for the period of gestation.¹ Various minimal hematologic standards for normal pregnancy have been proposed.^{1, 2, 3} For this study a hemoglobin of 10 Gm. per cent, a hematocrit of 33 per cent, and an erythrocyte count of 3.36 million per cubic millimeter were considered as the minimal normal values between the twelfth and the thirty-sixth week of pregnancy.²

Many observers have described satisfactory therapeutic results using iron preparations alone or in combination with other substances.^{1, 4, 5, 6, 7} Others have ascribed little efficacy to these agents.^{2, 8} In view of these discrepancies we feel that adequate comparison with simultaneously observed controls is lacking. As a result, this study was undertaken to review the cases of anemia of pregnancy followed at the Chicago Lying-in Hospital during the past several years.

Initial and periodic hemoglobin determinations are very important parts of prenatal and postpartum care. The usual methods for determining hemoglobin—either with the visual or photoelectric colorimeter—require very small amounts of blood, 0.02 ml. and dilutions of 100 to 400 times. Thus the combined error of the pipette and chamber, as well as the technician may be 7 to 15 per cent. The hematocrit and erythrocyte count are methods for determining the number of red blood cells per unit of blood. The hematocrit has a closer correlation with the hemoglobin concentration than the red cell count, because the error in the former is approximately 2 per cent, while the minimum error in the red cell count is over 8 per cent. For over ten years we have been using the hematocrit determination on heparinized blood as a screening method. Any patient who is less than twelve weeks pregnant or more than six weeks post partum whose hematocrit is less than 37 volumes per cent is referred to the antepartum anemia clinic. Between twelve weeks and thirty-six weeks gestation the lower limit of the hematocrit is 30, and between thirty-six weeks and term the lower limit is 32 volumes per cent. The procedure in the anemia clinic is to obtain additional history and special examinations as to possible causes for the anemia. A diet history is obtained in some instances. The hemoglobin,

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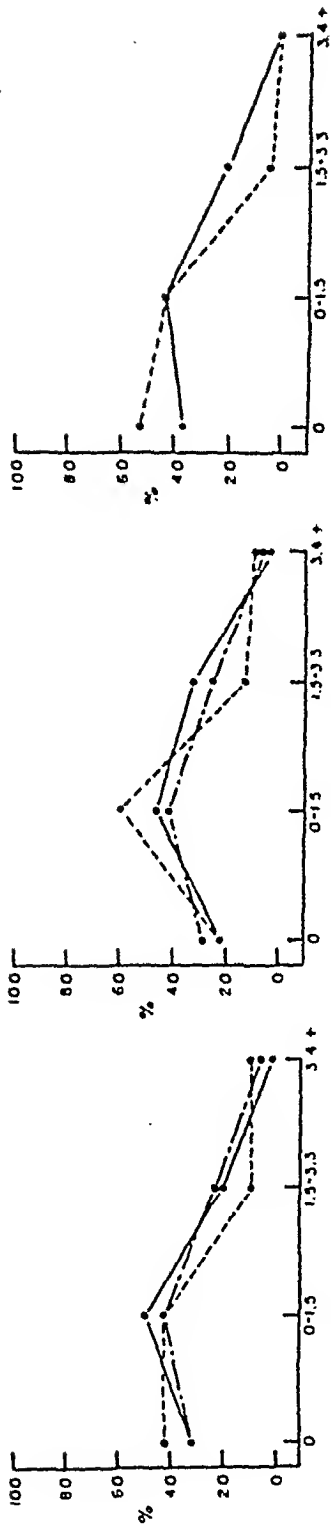


FIG. 1.

TABLE II

| COMPARISON OF TREATED GROUP WITH CONTROLS AT BEGINNING OF OBSERVATION PERIOD | | | |
|--|-------------|----------------------|--------------------------------|
| | MEAN AGE | MEAN NO. OF PREG. | MEAN WEEK OF PREG- NANCY |
| Untreated controls | 28.3 ± .5 | 3.2 ± .2 | 31.4 ± .4 |
| Treated group | 27.5 ± .3 | 3.2 ± .1 | 31.2 ± .3 |

TABLE III

| | MACROCYTIC | | MICROCYTIC | | NORMOCYTIC | |
|---------------|------------|-----|------------|-----|------------|-----|
| | Hb | SD* | Hb | SD* | Hb | SD* |
| Controls | 10.2 | 0.7 | 9.6 | 1.3 | 9.8 | 1.3 |
| Treated group | 11.1 | 1.4 | 10.6 | 1.9 | 11.3 | 1.7 |

*SD, Standard deviation.

hematocrit, red cell count, leucocyte count, and differential determinations are made. The various indices, mean corpuscular hemoglobin, and cell volume, etc., are determined and the anemia classified. For purposes of this study, all cases complicated by blood loss, toxemia, and infection were excluded.

After a preliminary observation period of two to six weeks during which the determinations were repeated, therapy was begun. All treated cases received iron in doses accepted to be adequate.⁹ Also, in certain of the cases accessory hematopoietic substances such as vitamins of the B complex, desiccated hog's stomach, and liver extract were administered in addition to the iron. In the graphs and tables these are included under the heading: Iron and Vitamins. After the institution of therapy the cases were followed at biweekly intervals until three to six months post partum with periodic blood studies. Patients with hemoglobin concentrations of six grams per cent or less were hospitalized for a more detailed study. In some cases transfusions of whole blood served as the principal therapy given or as a supplement to other treatment.

Results

Two hundred fifty cases were studied. These have been classified as to mean corpuscular volume⁹ and therapy administered (Table I). The mean corpuscular hemoglobin concentration⁹ was determined in each case, and it was found that 42 per cent were normochromic, 56 per cent hypochromic, and 2 per cent hyperchromic. At the time of their first visit 57 per cent of the entire group were anemic. This represented 61 per cent of the treated group and 48 per cent of the controls.

TABLE I

| | NO. OF CASES | GAIN OF Hb IN GM. IN 21 DAYS | | | | |
|-------------------|-----------------|--------------------------------|-----------------|-------------------|-----------------|------------------|
| | | A | B | C | D | E |
| | | DECREASED OR UN- CHANGED | 0 TO 1.5 GM. | 1.6 TO 3.3 GM. | OVER 3.3 GM. | MEAN GAIN GM. |
| Macrocytic | | | | | | |
| Controls | 12 | 5 | 5 | 1 | 1 | 0.82 ± .20* |
| Iron alone | 31 | 10 | 15 | 6 | 0 | 0.73 ± .09 |
| Iron and vitamins | 19 | 6 | 8 | 4 | 1 | 0.92 ± .15 |
| Transfused | 2 | | | | | |
| Subtotal | 64 | | | | | |
| Microcytic | | | | | | |
| Controls | 39 | 8 | 23 | 5 | 3 | 0.86 ± .09 |
| Iron alone | 53 | 11 | 24 | 17 | 1 | 1.24 ± .09 |
| Iron and vitamins | 32 | 9 | 13 | 8 | 2 | 1.04 ± .14 |
| Transfused | 9 | | | | | |
| Subtotal | 133 | | | | | |
| Normocytic | | | | | | |
| Controls | 25 | 13 | 11 | 1 | 0 | 0.24 ± 0.6 |
| Iron alone | 27 | 10 | 12 | 5 | 0 | 0.73 ± .12 |
| Transfused | 1 | | | | | |
| Subtotal | 53 | | | | | |
| Total | 250 | | | | | |

*Probable error of mean.

⁹Iron was prescribed in the following daily doses: Ferrous sulfate, 1.0 Gm.; Ferric ammonium citrate, 5.0 Gm.; or Ferrous Carbonate, 5.0 Gm.

Diet histories of forty-two patients were analyzed by our nutritionist. Using the National Research committee's criteria for iron, and Burke's criteria for protein, she classified the diets as follows: poor iron and poor protein intake—14 per cent; poor iron, fair protein—31 per cent; poor iron and good protein—17 per cent. Thus 62 per cent had a low intake of iron. However, these diets may not be as deficient as they seem to be because they were based on patients' estimates, and we have learned that they are inaccurate and that the food must be weighed and recorded immediately. We are now doing this.

In certain cases transfusions of whole blood served as the principal therapeutic agent as indicated above. In these, transfusions were given as emergency measures because of rapidly falling hemoglobin values. Also, in five of the controls and in eleven of the treated cases, transfusions were administered after the completion of the twenty-one-day observation period when the patient had reached term before the hemoglobin had returned to normal levels. No hematologic data on the transfused cases are included here, as blood was uniformly given in quantities adequate to bring the hemoglobin to normal levels.

Discussion

The plasma volume during pregnancy increases 25 per cent and the red cell volume only 23 per cent, thus accounting for the physiologic anemia of pregnancy.¹² Reported bone marrow studies have revealed a normal erythroid pattern, and served to confirm the concept that this condition arises from hydration alone.

The cases in the present study represent those in which the hematologic findings fell below the minimal physiologic values. Changes in the peripheral blood may reflect both pathologic and physiologic processes simultaneously and their detection is characterized by certain inherent errors.² As a result of these factors the effects of any therapeutic agent must be evaluated cautiously.

Classically, microcytic hypochromic anemias are associated with iron deficiency. During pregnancy an inadequate diet, defective absorption from the gastrointestinal tract, and increasing fetal demands have been accused of precipitating this condition. Wolff and Limarzi^{13, 14} report a normoblastic hyperplasia of the bone marrow in such cases. These workers and others^{1, 5, 6} conclude that these anemias are the result of an iron deficiency and can be corrected by administering simple iron salts. Some workers stress the importance of diet in their prevention and correction.^{1, 15, 17} Others indicate that although an adequate diet is important from the standpoint of maternal health, the quality of the diet has little effect on the hematologic findings except in the extremes.^{3, 8, 16} Changes in the gastrointestinal secretory function occur in most pregnant women,¹⁷ yet no significant correlation exists between the decreased gastric acidity and the incidence of anemia.³ Further, studies with radioactive materials during pregnancy have revealed that iron is absorbed at two to ten times the normal rate.¹⁸ The amount of iron necessary for fetal growth is negligible during the first twenty-eight weeks and yet it is during this period that there is the greatest fall in the maternal hemoglobin concentration. It is only during the last twelve weeks, when the fetal weight increases from approximately 1,000 Gm. at twenty-eight weeks to 3,400 Gm. at term, that the iron requirement of the fetus becomes appreciable. But even at term, when the actual amount of iron required by the fetus is greater, the total fetal content is only 280 mg., which could be furnished by the iron from 600 c.c. of maternal

During adequate therapy the expected rate of hemoglobin formation is 0.078 Gm. per day, and the maximum is reached between the second and fourth week.^{10, 11} For this reason a twenty-one-day observation period was selected in order to evaluate the effects of treatment. At the beginning of this period the treated group showed no significant differences from the controls (Table II).

The gain in hemoglobin concentration in the various groups during the three weeks of observation is recorded in Table 1 (Columns A to D). Inspection of these data reveals that the number of cases showing the expected gain in hemoglobin during this observation period, 1.6 Gm. in twenty-one days, is only slightly greater in the treated groups than in the controls. Fig. 1 presents these data in graphic form, the gain in grams of hemoglobin being plotted along the abscissa, and the percentage of cases along the ordinate. When the mean values in the separate groups are compared, the difference between the controls and the treated cases is not statistically significant (Table 1, Column E).

Comparison of the hemoglobin values of the treated groups and the controls at term failed to reveal any significant differences between the two (Table III). Further, while 51 per cent of the controls were anemic at term, 27 per cent of the treated group were still anemic at that time.

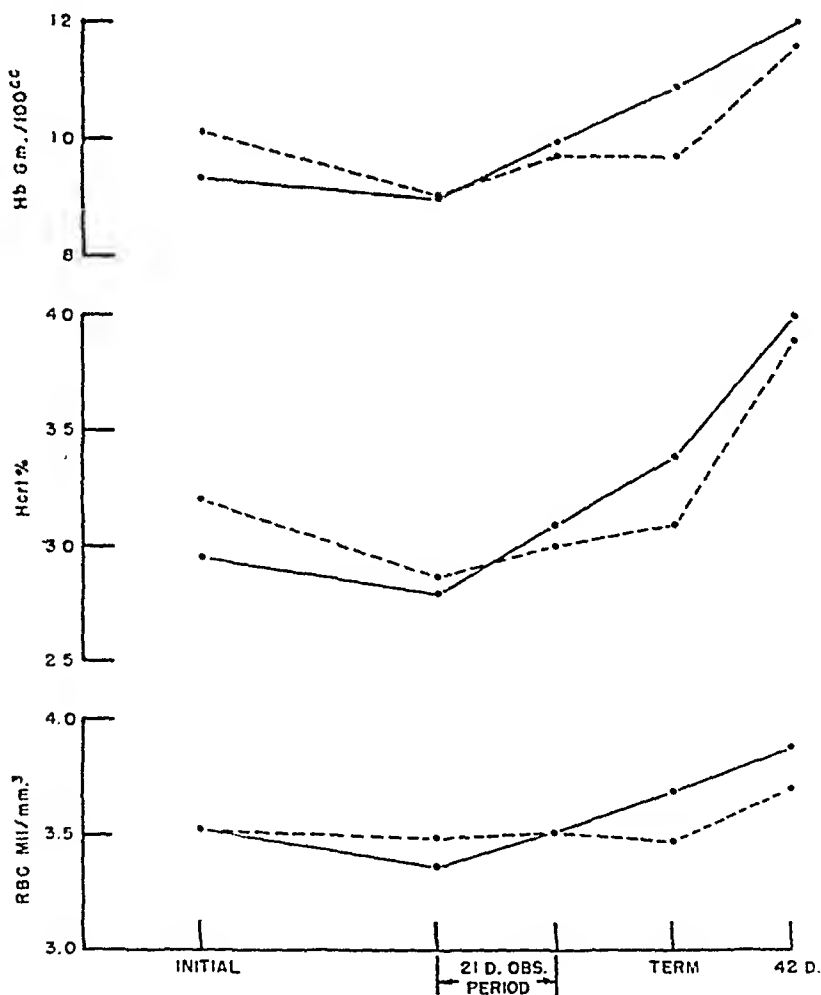


FIG. 2.

Many patients did not return for postpartum examinations, and therefore data were not uniformly available for comparison. The hematologic values of both groups, however, showed a rapid return to normal levels during this period (Fig. 2).

ANTENATAL BLOOD GROUP DETERMINATION*

A Preliminary Report

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IN THE course of a previous study¹ on isoimmunization with the A and B agglutinogens, it became apparent that a high anti-A or anti-B agglutinin titer in the serum of a pregnant woman is an indication of isoimmunization of the mother against the corresponding antigen in the fetus. In the case of a primipara, the immunization was naturally ascribed to the fetus of the existing gestation, while in the case of a multipara, either the existing gestation or any of the previous pregnancies could have acted as the immunizing agent.

In order to obtain more data on this hypothesis, a series of 100 pregnant women with blood groups O, A or B were chosen for study. Among them were 19 cases of heterospecific pregnancy. In each of the 100 cases, the anti-A and anti-B agglutinin titer of the serum was determined. As a control series, the bloods of 50 nulligravidas (O-A-B) who were never subjected to immunization by pregnancy or injection of blood were similarly titrated. In the pregnant women with children of blood groups compatible with their own, the average anti-A or anti-B titer of their serum did not exceed 1:500, and in no instance was the titer found to be above 1:1,280. In the series of nulliparas, about 95 per cent of the cases showed a titer ranging from 1:10 to 1:300. In no instance did the titer exceed 1:1,280. In neither of the latter two groups was there a single instance in which the anti-A or anti-B agglutinin titer reached a level of 1:2,000. In contrast to these values, the women with heterospecific pregnancy showed a much higher titer. In the majority of these instances it ranged from 1:500 to 1:5,000, and some reached values as high as 1:20,000 or more.² Titers of 1:2,000 or over were considered significant, since, as stated above, none of the nulliparas nor multiparas with babies of compatible blood groups showed such high values. Therefore, this titer was arbitrarily chosen as a base line above which any agglutinin titer would indicate isoimmunization against its specific antigen A or B. Thus, a woman of group B, whose serum showed an anti-A agglutinin titer of 1:2,500, was presumed either to be bearing (particularly of a primigravida), or to have previously borne a group A offspring. This presumption was confirmed in each case in which the agglutinin titer exceeded 1:2,000, as seen from Table I.

Comments

A study of Table I suggests that it may be possible to foretell the baby's blood group from a study of the titer of the group specific agglutinins in the serum of the mother. In several instances (not included in this table) in which the mother's serum showed an agglutinin titer approximating 1:2,000, but in which the mother was delivered of a group O baby, examination of her pre-

*Aided by a grant from the United Hospital Fund of New York City.

blood. Furthermore, it is during this last twelve weeks that the maternal hemoglobin concentration is either stationary or is increased. Thus, during the maximum fetal requirement, the hemoglobin concentration also increases.^{2, 8}

The results of the present study indicate that during pregnancy the rate of hemoglobin formation is not significantly altered by the administration of iron alone or in combination with accessory substances. In the light of the foregoing material this suggests that these anemias are not due to a simple iron deficiency, but that some other factor is lacking or that the defect lies in the mechanism of postabsorptive iron utilization.

The "pernicious-like" or megaloblastic anemia of pregnancy occurs only rarely.¹⁹ Several workers suggest that the diagnosis can only be made from studies of the bone marrow and that the peripheral blood findings are often misleading.^{13, 14, 20} It is unlikely that the macrocytic anemias in the present series are examples of the megaloblastic type of anemia.

Summary

Two hundred fifty cases of anemia in pregnancy were studied to evaluate the effects of treatment with iron alone and in combination with accessory factors. Controlled observations indicate that the administration of these substances does not increase the rate of hemoglobin formation significantly.

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The titers given are those obtained by the agglutination (saline dilution) technique. With the so-called conglutination technique (using homologous or AB serum as a diluent) much higher values were obtained in most, although not all of the cases. In fact, in a number of instances the "conglutinin" titer was considerably lower than the agglutinin titer.

Conclusions

1. In heterospecific pregnancies the anti-A and anti-B agglutinin titer in the mother's serum may rise to much higher levels than those found in nulliparas, or in mothers with offsprings of compatible blood groups.

2. When the anti-A or anti-B agglutinin titer in a primigravida's serum rises to a level of 1:2,000 or over, it may be presumed that the fetus in utero possesses in its blood the corresponding antigen A or B. In the case of a multipara, the immunizing A or B antigen will be found to be present in at least one of her previous children or in the offspring of the present pregnancy.

3. In primiparas and in certain multiparas with heterospecific pregnancy, the baby's blood group sometimes may be determined antenatally by the titration of the group specific antibodies in the mother's serum.

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TABLE I. ANTENATAL BLOOD GROUP DETERMINATION BY ANTIBODY TITRATION OF MOTHER'S SERUM (ANTI-A AND ANTI-B AGGLUTININ TITERS EXCEEDING 1:2,000)

| CASE NO. | NUMBER OF PREGNANCIES | MOTHER'S GROUP | TITER | CHILD'S GROUP |
|----------|-----------------------|----------------|--------------------------------------|---------------|
| 35 | 1 | O | Anti-B 2560 | B |
| 38 | 9 | O | Anti-B 20,480 | B |
| 39 | 1 | O | Anti-A 5120 | A |
| 42 | 0 | O | Anti-A 2560 | A |
| 43 | 2 | B | Anti-A 2560 | AB |
| 44 | 1 | O | Anti-A 5120 | A |
| 76 | 1 | A | Anti-B 2560 | AB |
| 86 | 1 | O | (Anti-A 5120) (Anti-A Milk 5120) | A |
| 88 | 1 | O | Anti-A 20,000 | A |
| 103 | 2 | O | Anti-A 5240 | A |
| 110 | 3 | O | Anti-A 5120 | A |

vious offsprings showed them to belong to group A, B, or AB, as the case may have been. While a titer lower than 1:2,000 in a group O mother did not exclude the possibility of a group A or B offspring, the reverse was not true. No instance was found in which a mother with an agglutinin titer of 1:2,000 or over did not have an offspring with the corresponding specific antigen. Admittedly, the present series is not a very large one, but the nonstatistical evidence thus far may be considered quite striking. A case in point is case 43. The mother here is a group B, and therefore normally should have anti-A agglutinin in her serum. But the fact that the titer of the agglutinin was found to be as high as 1:2,500 led to the presumption that the offspring in utero must possess the A antigen, since, as far as could be determined, the mother had not been exposed to immunization with the A antigen previously. As is seen from Table I, this was a correct presumption, since blood grouping tests after birth proved the child to be a group AB. That this reasoning is equally applicable to instances of anti-B agglutinin, is borne out in case 76, where the anti-B agglutinin in a group A mother was found to be 1:2,560. The prediction that the yet unborn offspring contained the B antigen was confirmed, the child having been found to be a group AB at birth. Incidentally this baby was a girl, one of a twin, the other being a boy and a group A.

The highest titer in the tabulated cases was 1:20,000 or slightly above. This value was found in one case of a primipara and in another of a multipara (a para ix), showing that the titer of the antibody does not depend upon the number of pregnancies.

Case 86 showed an anti-A agglutinin titer of 1:5,120 in the milk as well as in the serum; hence (as in the case of Rh isoimmunization) the contraindication for breast feeding these infants.

The preponderance of group O mothers in the above table is probably a haphance in this particular group of selected heterospecific pregnancies. Group AB, of necessity, had to be excluded from this series, since there are no anti-A or anti-B agglutinins in their serum.

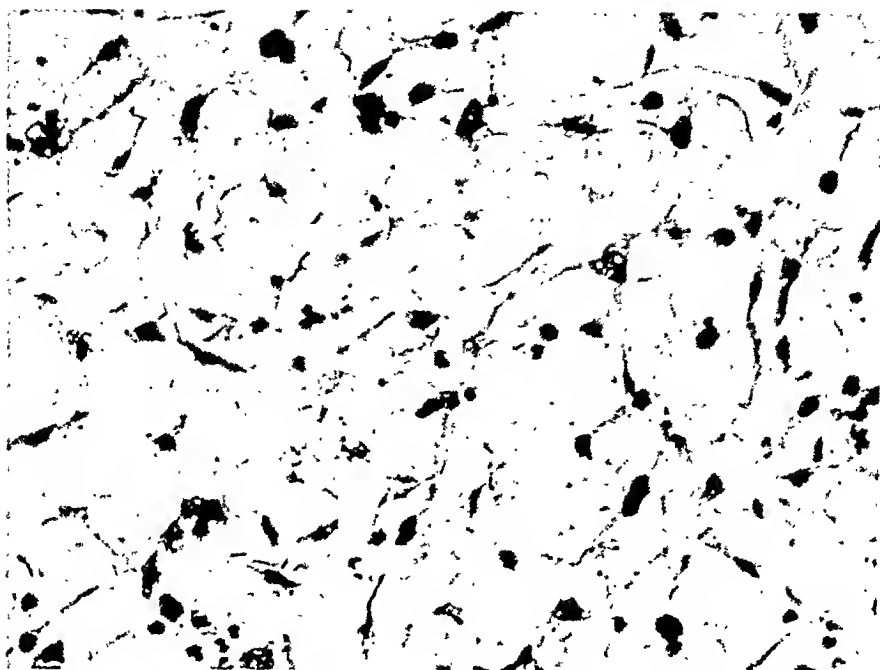


Fig. 1.—Myxomatous connective tissue network (Bodian $\times 235$).

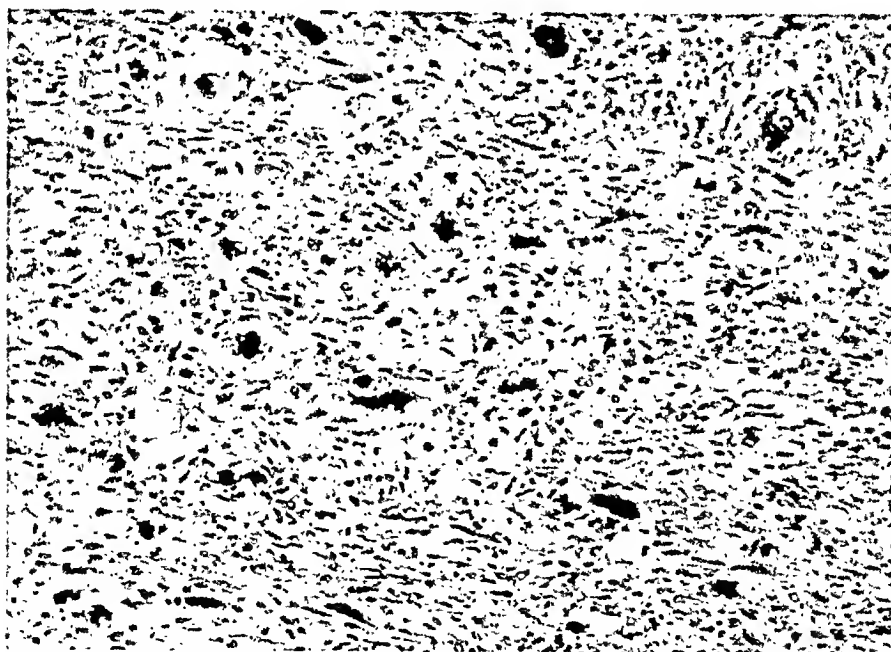


Fig. 2.—Plump spindle cell stroma with giant cells (hematoxylin and eosin $\times 100$).

Histologically the greater part of the tumor consisted of myxomatous connective tissue: spindle and star-shaped cells connected by delicate strands to form a network (Fig. 1). In other more cellular areas plump spindle cells with prominent nuclei and nucleoli and with mitotic figures were seen; interspersed were multinucleated tumor giant cells with large, often deeply staining nuclei and scanty cytoplasm (Fig. 2). Still other cellular areas showed rather irregular, round, or elongated cells, many with longitudinal striations and some with well-defined cross striations (Fig. 3): young striated muscle cells; scattered among these were embryonic myoblasts, large, often multinucleated cells

MESODERMAL MIXED TUMOR OF THE VAGINA: REPORT OF CASE

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THE following case, while primarily a pathologic problem, presents features of interest to the clinician as well. This report is of the third mesodermal mixed tumor diagnosed at the Mayo Clinic, two cases of such a tumor of the uterus having been reported by McDonald, Broders and Counseller; the tumor in the case reported herein is the first such tumor of the vagina found here.

Report of Case

A white child, 33 months of age, was admitted to the clinic on Nov. 6, 1946. Obstetric and family histories were irrelevant. About November, 1945, the parents had noticed the child scratching the vulva and saw a little blood. Examination by their local physician in February, 1946, had revealed a small tumor presenting at the vulva. The tumor was excised in March, 1946; the histologic diagnosis was "botryoid sarcoma (rhabdomyoma) of the vagina." The operative site received radium therapy seven months prior to her admission to the clinic, and the radium therapy was followed by roentgen therapy over a period of about two months. The child was apparently well for another two months but then more vaginal bleeding was noted and she was given further roentgen therapy. On admission to the clinic she presented no actual signs of distress, but the parents said she held back urine as long as possible. A satisfactory examination was not possible as the child was too apprehensive, but a soft mass was palpated in the vagina.

At operation on Nov. 8, 1946, a soft, polypoid tumor mass was found completely filling the vagina. The mass was removed, for the most part, and was found to originate on the right anterior wall of the vagina over an area of 5 by 2 centimeters. Because of the malignant nature of the tumor, as confirmed at operation by examination of a fresh frozen section, and its infiltration of at least the vaginal wall, the surgeon did not feel that a sufficiently radical operation could be attempted. The patient was discharged a few days later in good condition, but the parents were told that the prognosis was extremely grave.

Pathologic Findings.—The tumor, in pieces, weighed 24 Gm., forming an aggregate mass about 2.5 by 6 by 4 centimeters. It had the appearance of a group of polyps each about 2 cm. in diameter, the classical so-called botryoid morphology. The surface was smooth and gray-white except for a few hemorrhagic areas. The tumor was of firm consistency and could be cut easily; the cut surface was homogeneous and glistening.

Representative portions of the tumor were fixed in 10 per cent solution of formalin (3.8 per cent solution of formaldehyde), absolute alcohol, and Zenker's solution. Paraffin sections were stained by hematoxylin and eosin, Masson trichrome, Bodian and elastin H methods; sections also were stained for mucin by a modified Mayer mucicarmine⁴ method and for glycogen by the Best carmine method.

Mesodermal mixed tumors form an ill-defined group of malignant neoplasms of the uterus, cervix, and vagina. By definition they are monodermic in origin, as opposed to the origin of teratomas which is tridermic, they develop from mesoderm and they consist of heterotopic and highly malignant tissues.

The literature contains confusing reports as to the nature and incidence of these tumors. McFarland,¹² in an extensive review of the subject, listed 116 different names from the literature for mesodermal type tumors of the genital tract; among the best known was the term "botryoid sarcoma" after the "traubiges Sarkom" of Pfannenstiel (1892). McFarland suggested the name "dysontogenetic tumors" for the whole group. The bulk of his data is not in the literature, but Amolsch would seem to have reviewed it when he reported 447 cases of mesodermal mixed tumors of the uterus, cervix and vagina, so diagnosed on the basis of the presence of embryonic myxomatous tissue. He and subsequent writers followed the terminology of Kehler and called them all "mesodermal mixed tumors." Lebowich and Ehrlich² and Ehrlich³ limited the group sharply by demanding the finding of embryonal striated myoblasts in accordance with the criteria set forth by Låwen; they could find reports of but fourteen such tumors of the body of the uterus in the literature. Glass and Goldsmith were not quite so exacting in their requirements and found records of ninety-four mesodermal mixed tumors of the uterine body and cervix. The incidence of the vaginal group is even more uncertain. Kehler listed reports of nine vaginal sarcomas of children that showed heterotopic mesodermal tissues, usually embryonal striated muscle cells. McFarland,¹¹ in 1911, found reports of thirty-four "botryoid vaginal sarcomas," and by 1935¹² he had raised this figure to seventy-four. Bergström, in 1936, added twenty to McFarland's original thirty-four cases. Undoubted new cases have been reported infrequently in the last twenty-years; we could find but seven in the literature,^{1, 2, 12, 18, 19} and none since 1939. It is apparent that the wide variation in all these figures is due to differing criteria of diagnosis; this variation does not, however, detract from the interest in, or the importance of, the group.

The consensus as to etiology favors a theory of cell rests²⁰ that is, the persistence in the genital tract, of pluripotent embryonal mesenchymal cells, capable of producing varied mesenchymal tissues. Some investigators,^{15, 17} however, favor a theory of metaplasia. Thus McDonald, Broders, and Counseller suggested that these tumors arise by a process of dedifferentiation of the endometrial stroma cells, after which differentiation takes place into various types of mesodermal structures. In both of their mesodermal mixed tumors of the body of the uterus they could trace the development of fibroblasts of the endometrial stroma into cartilage, and they considered these tumors to be true endometrial sarcomas.

Mesodermal mixed tumors are found in the uterine body, cervix, and vagina. Those of the uterine body are commonest in the menopausal or post-menopausal age groups, those of the cervix are commonest in the reproductive period, while those of the vagina have all occurred in very young patients, mostly those less than three years of age.

Because of the varying criteria of diagnosis, it is difficult to assess the relative incidence in the various sites. Glass and Goldsmith gave the ratio of those in the body of the uterus to those in the cervix as 1.6:1, while Lebowich and Ehrlich, with their stricter criteria, gave a ratio of 1:3. Shaw found those of the body of the uterus slightly less common than those of the cervix, a ratio of about 1:1.5. As has been indicated, the number of vaginal tumors is uncertain, but they would seem to be the most common of the three.

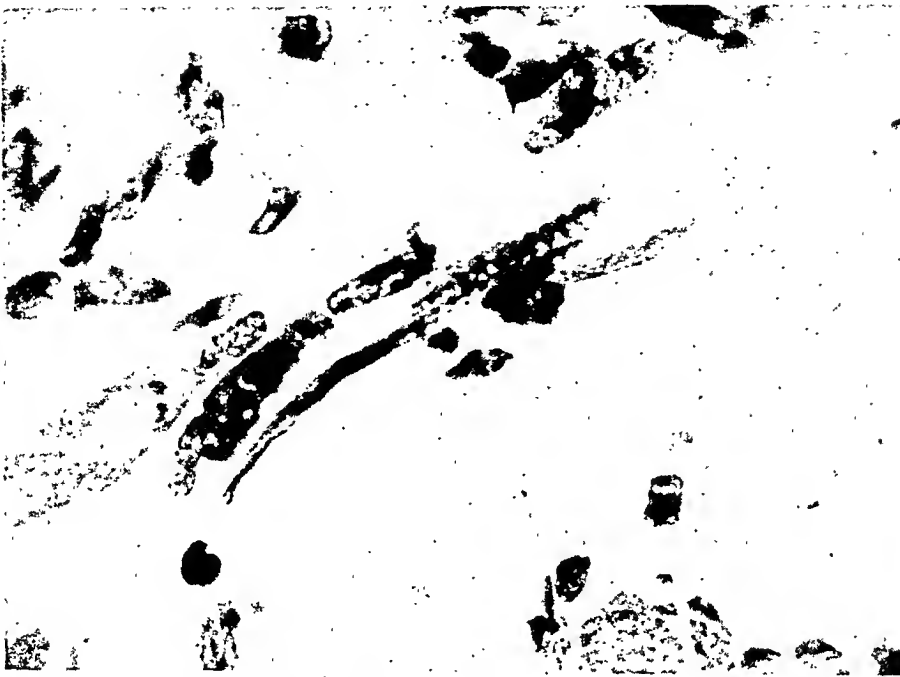


Fig. 3.—Young striated muscle fiber (Bodian $\times 1,000$).

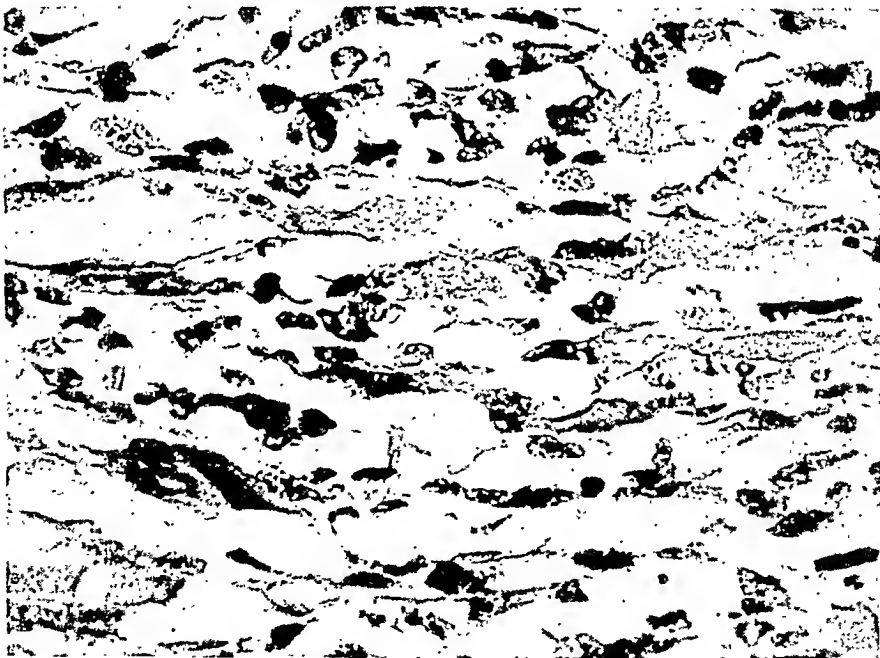


Fig. 4.—Myoblasts with myxomatous tissue matrix (Bodian $\times 430$).

with a relatively large amount of granular cytoplasm (Fig. 4). Some areas showed a considerable amount of collagen, but no cartilage or bone was found in the sections examined. Adult type squamous epithelium covered the surface of the tumor. Staining for mucin gave positive results in the myxomatous appearing areas and some extracellular and intracellular glycogen was noted. A few blocks showed gross degeneration with hemorrhage, and infiltration with acute and chronic inflammatory cells, doubtless a consequence of the radiation therapy.

In the present case the diagnosis was made early, but in spite of local excision and radiation therapy the tumor advanced rapidly. In the light of reports in the literature and in view of the very malignant nature of these tumors, it would seem extremely doubtful that even radical operation, performed when the diagnosis was first made, would have altered, in any way, the course of the disease.

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Clinically, there is little that is extraordinary about mesodermal mixed tumors. The signs and symptoms closely resemble the rather vague ones associated with adenocarcinoma of the genital tract of women, vaginal bleeding and discharge being the commonest signs. Such tumors of the vagina may first be noticed when they present at the vulva.

Grossly, mesodermal mixed tumors of the uterus appear often as single or multiple polyps, while the cervical and vaginal tumors may resemble a bunch of fused polyps, the grape-cluster effect that led earlier observers to name them "botryoid sarcomas." It should be noted that a single polypoid mesodermal mixed tumor may be indistinguishable grossly from a benign polyp of the genital tract.

The microscopic picture varies greatly with the individual tumor, and there is no constant difference between those of the uterus, cervix and vagina, except that neither bone nor cartilage has been found in those of the vagina.^{10, 18} They are true mixed tumors and contain numerous elements of mesodermal origin. All observers have agreed on the presence of myxomatous tissue, though not all have agreed on its nature; probably, however, it is embryonal mesenchymal tissue.²⁰ In addition there may be cartilage, striated and smooth muscle, myoblasts, bone, and so forth. Glandular structures, even adenocarcinoma, have been reported as occurring in the uterine tumors,^{5, 8, 9, 13, 15} but these were probably incidental inclusions of benign or malignant endometrial glands.^{13, 18} The histologic diagnosis of mesodermal mixed tumor may be difficult and many sections may be necessary to demonstrate heterotopic mesodermal tissue. As has been indicated, definite diagnostic criteria have not been universally accepted, but we agree with Morehead and Bowman¹⁴ in the belief that it is unwise to exclude all but those containing striated myoblasts since mesodermal mixed tumors are a pathologic entity and a group clinically.

The prognosis in all three types is uniformly bad, regardless of therapy. The over-all mortality rate has been given as 95 per cent¹; only one five-year and one ten-year cure have been recorded.⁶ The tumors have a marked tendency to local recurrence and extension after even the most radical operation, and death from local extension or from general metastasis may be expected to occur in six to twelve months.^{1, 6, 9} Metastasis to distant sites is, however, a relatively infrequent occurrence.^{1, 16}

Comment

The case reported herein would seem to be a typical example of a mesodermal mixed tumor of the vagina. Besides a myxosarcomatous stroma, the tumor contained myoblasts and striated muscle fibers, thus qualifying for the diagnosis in its most limited sense.^{8, 9} The occurrence of a positive result in staining for mucin which refutes Pfannenstiel's contention that the so-called myxomatous tissue is actually mere edema, has been reported also by previous observers.^{9, 15} The presence of glycogen is further evidence of the embryonic nature of the tumor tissue.

This case has been presented because of the rarity of the condition and to bring the entity to the attention of clinicians and pathologists alike. On gross, and even on microscopic examination, such a tumor, seen at an early stage, might easily be dismissed as a degenerating simple polyp, only to have the patient return with an infiltrating neoplasm obviously of high-grade malignancy. This has been a frequent occurrence in the recorded cases and may explain, in part, the extremely high mortality rate.

Memorial Hospital, was about 5 cm. in diameter with a hard, nodular surface that was beginning to ulcerate in places. The uterus was moderately movable, but there seemed to be some "shortening of the right parametrium." Biopsy report by the late Dr. James Ewing stated "epithelioma, type uncertain" (Fig. 1). Treatment consisted of 100 mc. hours of radon administered in each of three positions by vaginal bomb on April 17, 1922, and 3,000 mc. hours administered by platinum cervix tandem on the following day. This was followed by a cycle of low voltage pelvic x-ray to two anterior and two posterior fields on April 19 and 20. The patient remained under the observation of the gynecologic department of the Memorial Hospital for twelve and one-half years, until Nov. 21, 1934. There was no evidence of residual or recurrent tumor during this period.

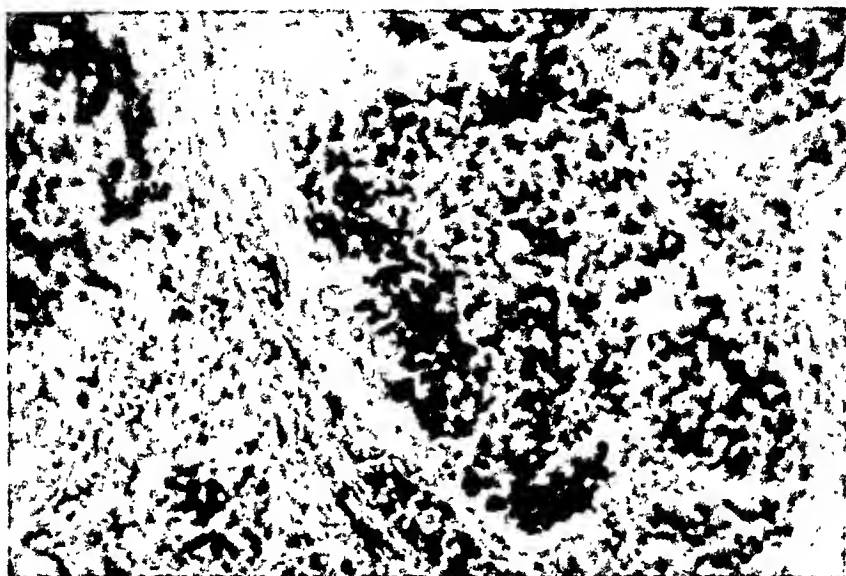


Fig. 1.—Case 1. Cervical biopsy specimen, showing anaplastic epidermoid carcinoma.

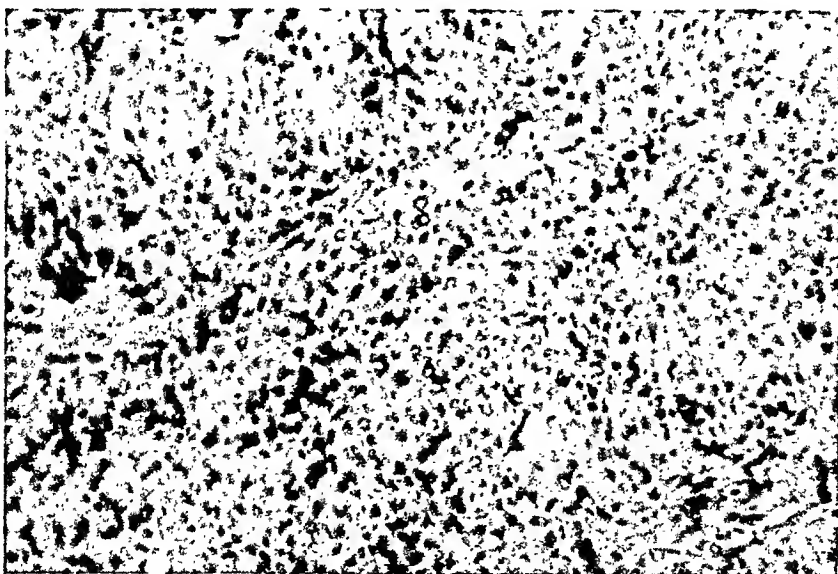


Fig. 2.—Case 1. Cervical tumor removed at autopsy seventeen and one-half years later, showing same cell type as original biopsy.

LATE RECURRENCE OF CERVICAL CARCINOMA FOLLOWING RADIATION THERAPY

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(From the Gynecological Service of the Roosevelt Hospital)

MORE than one-half of the patients with carcinoma of the cervix who have been unsuccessfully treated by irradiation at the Roosevelt Hospital showed a recurrence of their tumor within a year following treatment. Tumor recurrence after five years is distinctly unusual. This fact has served as the justification for the reporting of cervical cancer statistics in terms of five-year cures. Most gynecologists consider patients completely cured who survive this period with no clinical evidence of the disease.

Cervical cancer does not always run so rapid a course, however. New concepts of the pathology and biology of the early stages of the disease have been developed during recent years. Lesions which formerly were considered benign or of questionable malignancy have been associated with genuine cancer sufficiently often, either by the observation of the untreated patient during the ensuing years after biopsy, or by more intensive examination of the original specimen to merit the diagnosis of cancer themselves.

Smith and Pemberton (1934) reported one case in which six years elapsed between the original biopsy, which later was diagnosed pathologically as carcinoma, and the development of the lesion to the readily recognizable clinical entity; and in another they reported an incubation period of possibly twelve years. In a case reported by Stevenson and Seipiadès (1938) clinical cancer of the cervix did not appear until eight and one-half years after the microscopic diagnosis of noninvasive carcinoma. More recently Taylor and Guyer (1946) have described another case in which seven years elapsed between a positive biopsy and the ultimate diagnosis of clinical carcinoma. It has been shown by Te Linde and Galvin (1944) that lesions diagnosed as intraepithelial carcinoma, noninvasive carcinoma, or carcinoma in situ, previously believed by some pathologists to be only precancerous, usually are found to contain regions of invasiveness if the specimen is sectioned serially. These observations strongly indicate that cancer of the cervix may develop quite slowly in its very early stages.

The purpose of this communication is to record two extraordinary cases which show that cervical carcinoma may progress slowly, or perhaps even lie dormant for long periods after treatment by irradiation, during its later clinical stages.

CASE 1.—A. G. (R. H. No. 394167) was a 52-year-old white nulliparous divorcee with a history of four spontaneous abortions. She was treated for primary carcinoma of the cervix in April, 1922, at the age of 35 years, at the Memorial Hospital. Her cervix at that time, according to a report from

few years, since 1936, she had experienced a foul, blood-tinged vaginal discharge, although she had not menstruated since her previous radiotherapy. Pelvic examination disclosed a hard, friable tumor mass which involved the cervix and adjacent vaginal walls with slight fixation of the parametria. Biopsy of the cervical tumor showed epidermoid carcinoma, grade III. The surface epithelium was ulcerated by a neoplastic growth composed of squamous epithelium with limited keratinization. The cells were loosely arranged, had large nuclei, and numerous mitoses (Fig. 3). The patient's serologic tests for syphilis were positive. During the next few weeks she received twenty deep x-ray treatments through four pelvic portals, a total dose of 6000 r. Several episodes of vaginal bleeding occurred in the course of this treatment, each being managed with vaginal packing and blood transfusion. She received antisyphilitic therapy with bismuth at the same time. The patient was readmitted on Feb. 12, 1945, because of abdominal cramps, weight loss, uremia, and anemia. The tumor had extended to the bladder and rectum with the formation of a vesicovaginal fistula and a rectovaginal fistula. Cystoscopic examination indicated blockage of the right ureter by the tumor. The patient died on May 16, 1945.

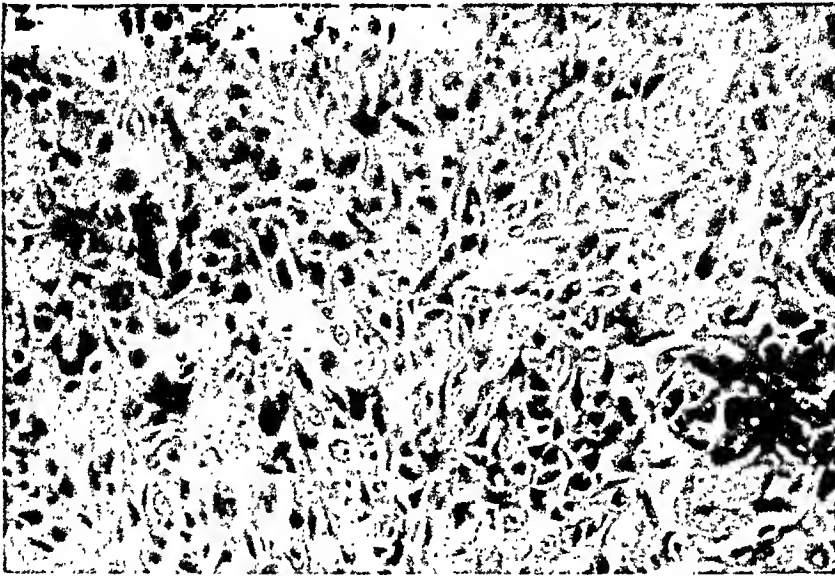


Fig. 3.—Case 2. Cervical biopsy specimen, showing epidermoid carcinoma, nineteen and one-half years after treatment.

Comment

It is impossible to prove that the secondary cervical tumors in these two cases represent recurrences rather than independent cancers. The fact that the histologic types of the secondary tumors correspond with those of the original biopsy specimens makes the presumption reasonable, however, that we are dealing with long delayed recurrences of previously treated cervical cancers. This presumption is strengthened in Case 1, because of the anaplastic nature of the tumor. Since this is the least common of the epidermoid cervical cancer types the chances of an independent new growth of the same type are small. Covington (1947), in reporting recently a similar case of recurrent carcinoma of the cervix seventeen and one-half years after radiation therapy, said that he had never seen a new cancer develop in a cervix which had been treated previ-

She was admitted to the Roosevelt Hospital Sept. 21, 1939, complaining of vomiting, diarrhea, and lower abdominal pain of eighteen days' duration. A hard, irregular, movable mass, about 15 cm. in diameter, occupied the right lower quadrant of the abdomen. The vagina was constricted and filled with hard friable tumor. Biopsy of this tumor showed only granulation tissue. The patient's serologic tests for syphilis were positive. Her blood urea nitrogen was 85 mg. per 100 c.c. the day after admission and rose in three days to 115. Intravenous pyelograms showed no excretion of the dye from either kidney. The patient developed a toxic erythema and died Oct. 18, 1939.

At autopsy the anatomic diagnosis was "cervical carcinoma, primary in cervix, with extension to fundus, bladder, rectum, ovaries, Fallopian tubes, and metastatic invasion of periaortic lymph nodes, liver, and diaphragm; ureteral obstruction, bilateral, with hydronephrosis and hydronephrosis." The pelvic organs were greatly distorted by infiltration of the tumor. The outline of the cervix was destroyed by ulceration and necrosis, the process extending into the vaginal walls. More than three-fourth of the uterus was involved in the tumor mass. The endometrium was thin and smooth except for a single small polyp. Microscopically the tumor showed irregular masses of undifferentiated oval cells supported by small amounts of stroma, with almost complete lack of organization. The nuclei were hyperchromatic and mitoses were fairly numerous (Fig. 2). Dr. Walter Brandes, Pathologist to the Roosevelt Hospital, and Dr. Ewing compared sections of this tumor with that of the original cervical biopsy of seventeen and one-half years previously and agreed that they could not distinguish the one from the other, so completely similar were they in histologic detail.

CASE 2.—N. M. (R. H. No. 13502 and No. 28803), a 33-year-old married Jamaican Negro woman with two children, was admitted to the Roosevelt Hospital for the first time on April 1, 1925, complaining of dysmenorrhea and intermittent backache and vaginal discharge for two years. Her menses were regular, her last period having begun March 24. Her cervix was large, bilaterally lacerated, eroded, and a thick purulent discharge was in the canal. The fundus was of normal size, retroverted, and a small fibroid was present near the right cornu. On April 6, 1925, curettage, tracheloplasty (Schroeder), left salpingo-oophorectomy, hysteropexy (Simpson), and appendectomy were performed. Chronic salpingitis was encountered. Histologic examination of the two pieces of cervical tissue removed at operation revealed epidermoid carcinoma. The original specimen, unfortunately, could not be found for re-examination, but the pathologic report, which is quoted herewith, leaves little doubt as to the accuracy of the diagnosis: "Sections of the cervix through the region of the external os show well-preserved stratified squamous epithelium and a few typical cervical glands. In addition round masses of neoplastic epithelial cells are present some distance beneath the surface epithelium. Individual cells show pale staining cytoplasm; the nuclei vary in size and shape and are hyperchromatic. Mitoses are present. Occasionally a small cord of these cells lies free in connective tissue spaces. Lymphocytes surround the tumor. Some of the epithelium is keratinized. The tumor masses invade the cervical glands in some places." On April 16, 1925, 50 mg. of radium was applied in the cervical canal for twenty-four hours; and between April 20 and July 14 the patient received a filtered x-ray treatment through each of six pelvic portals, with the 200 kv. machine at a skin-target distance of 50 cm.—three exposures for thirty minutes each, and three for forty minutes.

Following her discharge from the hospital the patient returned at regular intervals to the Out-Patient Department until 1931. She was not seen again until Nov. 9, 1944, at the age of 53 years. She now stated that during the past

Special Article

PELVIC CANCER DELAY*

The Organization and Observations of the Philadelphia Committee for the Study of Pelvic Cancer

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THE high death rate from cancer today emphasizes the ignorance of its cause, the limitations of present forms of therapy, and the failure to diagnose it while still favorable for treatment. What measure of success we enjoy is limited to that small group of fortunate patients in whom an early diagnosis is achieved. A greater effort must be made to prevent its development and to find it at its inception.

The problems of making an early diagnosis of cancer have long been recognized. For instance, the very location of a malignant growth often precludes our ability to find it. In contrast, accessible lesions afford no reasonable excuse for delay in their early discovery. Most malignancies occurring in the female pelvis fall into this latter category. Basically, therefore, the early discovery of cancer so located is dependent on the prompt action of the patient at the first sign of trouble; and likewise on the physician's immediate discharge of his duty at her first visit.

It has been shown frequently that the physician is an important factor contributing to delay in the early diagnosis of cancer. The very life and death of an individual may depend on the physician's degree of suspicion of cancer, his ability to recognize its early stages, and upon his ultimate recommendation. If, as it seems, the physician is a contributor to delay in the diagnosis of early cancer, then something beyond mere criticism is indicated. Remedial suggestions have been made many times, but no practical educational program for the general practitioner or physicians in general has ever been established.

Two years ago a group of physicians in Philadelphia proposed a plan whereby they hoped to stimulate physicians to recognize their responsibility in regards to the diagnostic delay period in patients suffering with pelvic cancer. In brief it was proposed:

1. To form a committee of gynecologists who would study all pelvic cancer cases in Philadelphia with special reference to the sequence of events occurring between the onset of the patient's first symptoms, a definite diagnosis and adequate treatment.

2. To utilize the facts obtained from this study to inform the medical profession of their importance in diminishing the delay in diagnosis of pelvic cancer.

*Read before the Philadelphia Obstetrical Society, Feb. 6, 1947.

ously by radium. These two cases, therefore, are submitted as recurrent cervical cancers which appeared seventeen and one-half years and nineteen and one-half years after initial treatment, respectively. Covington's case and the present two represent the latest local recurrences of epidermoid carcinoma of the cervix of which I have been able to find record.

From a practical clinical standpoint it would seem safe to consider as probably cured any patient with cervical cancer who survives the standard five-year period without evidence of recurrence. Records of the Roosevelt Hospital contain 105 cases, exclusive of the 2 above, in which the time of recurrence could be determined in patients treated with radium. The time intervals are shown in Table I. The average time of recurrence was 14.5 months. Fifty-seven per cent of the recurrences were detected within a year of treatment, and only one recurrence was observed after five years.

TABLE I. INTERVAL BETWEEN TREATMENT AND RECURRENCE IN 105 CASES OF RECURRENT CERVICAL CARCINOMA

| INTERVAL (MONTHS) | NUMBER | PER CENT |
|-------------------|--------|----------|
| 0- 6 | 37 | 35 |
| 7-12 | 23 | 22 |
| 13-24 | 28 | 27 |
| 25-36 | 8 | 8 |
| 37-48 | 7 | 7 |
| 49-60 | 1 | 1 |
| over 60 | 1 | 1 |

Summary

The average interval between treatment and recurrence in 105 patients with recurrent epidermoid carcinoma of the cervix treated with radium was 14.5 months. Fifty-seven per cent of the patients manifested their tumor recurrence within a year. Only one recurrence was observed after five years. Two additional cases are reported in which local recurrence of previously irradiated cervical cancer occurred seventeen and one-half years and nineteen and one-half years later, respectively.

Addendum: The present data are at variance with a recent report by D. G. Morton (Am. J. Roentgen. 57: 685, 1947). Of 45 patients with cervical cancer who survived five years after irradiation therapy, 13 (29 per cent) subsequently died of cancer.

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delay by the physician is disclosed, little emphasis and importance are placed on this in itself. The underlying reason for the delay is the important topic of discussion. For example, when the delay resulted from failure to take a biopsy, the discussion will evolve around the question of whether a general practitioner should attempt cervical biopsy. If so, what equipment should he have available? Should he biopsy all cervixes showing erosion? How should he decide the need of a biopsy? At the conclusion of the discussion, the helpful suggestions and the constructive criticism have been a lesson to all present. The physician who failed to take the biopsy has been forgotten, and this is as it should be.

Summary of Results

Between Nov. 1, 1945, and Jan. 1, 1947, some 455 living patients with pelvic cancer were investigated. Of this number, in 145, or 31.8 per cent, there had been no delay. The remaining 310, or 68.1 per cent of the cases, demonstrated a lapse of one or more months from the time the symptoms were first noted until a correct diagnosis was made and adequate treatment instituted.

| | | |
|------------------------------|-----|-------|
| Number of cases investigated | 455 | |
| No delay | 145 | 31.8% |
| Delay of more than one month | 310 | 68.1% |

Of these 310 cases showing a delay it was found that the patient alone was responsible in 197, or 63.6 per cent; the physician alone was at fault in 76, or 24.5 per cent, of the cases. In 37, or 12.0 per cent, of the cases, the patient and the physician were equally dilatory. Thus the combined total involving the physician was 113 cases, or 36.5 per cent.

| | | |
|-------------------------------|-----|-------|
| Number of cases showing delay | 310 | |
| Responsibility— | | |
| Patient | 197 | 63.6% |
| Physician | 76 | 24.5% |
| Physician and patient | 37 | 12.0% |

In 93, or 82.3 per cent, of the cases, one physician contributed to the delay. In 17, or 15.0 per cent, of the cases, two physicians were involved in the delay of each patient. Three physicians were dilatory in three of the cases, or 2.6 per cent. It should be noted that in the 113 cases showing physician delay there was a total of 136 doctors responsible—which truly is a more revealing index of the problem at hand.

| | | |
|---|-----|-------|
| Number of cases showing physician delay | 113 | |
| Delay by one physician | 93 | 82.3% |
| Delay by two physicians | 17 | 15.0% |
| Delay by three physicians | 3 | 2.6% |
| 136 physicians involved in 113 cases | | |

These figures demonstrate that the physician plays an active part in the problem of a delay in early diagnosis. Thus in a small way a program has been launched for educating the physician (be he specialist or general practitioner) to the opportunity afforded him to make an early diagnosis in cases of pelvic cancer. The Committee believes that such a program can become an influential contribution for obtaining earlier diagnoses in pelvic cancer and thus a better salvage of patients afflicted with this disease.

The project was accepted and sponsored by the Philadelphia Obstetrical Society. Such a committee was appointed and received the approval of both the Philadelphia Department of Public Health and the Philadelphia County Medical Society. Headquarters were established in the County Medical Society Building and the American Cancer Society granted funds, sufficient to permit the employment of a full-time investigator to carry out the actual work.

The principal hospitals of Philadelphia soon gave their full cooperation to this undertaking. They granted permission for the Committee's investigator to enter their wards and out-patient clinics for direct questioning of each patient suffering with pelvic cancer. At the present time the Committee has access to such patients in 19 different institutions, which include all of the teaching hospitals. A questionnaire designed for its brevity, clarity, and chronological disclosure of facts about the delay period has been used to help correlate and record the desired information.

Method of Utilization of Material

The Committee meets monthly. Prior to each meeting the cases investigated during the preceding month are classified into two main groups: those cases revealing no delay and those cases with an apparent delay. The cases with an apparent delay are then subdivided into three categories: (1) delay due to the patient, (2) delay due to the physician, and (3) delay due to both the patient and the physician. The cases showing physician delay are further scrutinized for detailed discussion at the time of the next meeting.

In March, 1946, the custom was instituted of inviting any physician intimately connected with the cases exhibiting delay to meet with the Committee to participate in the discussion. This was necessary for two reasons: The information obtained by our questionnaire was entirely that voiced by the patient. Knowing the frequent inaccuracy of patients' statements the Committee felt that in no case should the responsibility for delay be ascribed to a physician without affording him the opportunity to present the facts as he knew them. The second reason for inviting the family physician, and the main one, was to begin a program of education among the physicians of this city. Specifically the group wished to create a higher index of suspicion for pelvic cancer, emphasizing the importance of making adequate pelvic examinations and early diagnoses. The Committee was anxious to reveal the true causes of physician delay as they were brought to light by the survey and to take active steps to correct them.

Getting the busy doctor to attend the meetings at first posed a problem, since no physician is anxious to be censured or questioned as to his efficiency in the handling of his patients. In order to reach the physicians in question, a letter was written to each one, inviting him to attend the meetings to further disclose the details of the case history as he knew it. It was explained that the purpose of the Committee was not to ridicule or castigate anyone, but it was necessary to obtain all the facts before determining the existence of a true delay or what could be done to prevent a similar delay in the future. To date twenty-seven physicians have met with this Committee. The response and cooperation of these physicians have been most encouraging.

The meetings have been informal and friendly, yet the discussions have been serious and stimulating. The physicians who have met with the Committee have been dealt with in a friendly way and there has been a mutual exchange of ideas between the general practitioners and the specialists in Gynecology. When a

Since the liver and kidney lesions are not peculiar to eclampsia—pre-eclampsia, and, since the Goldblatt kidney does not produce eclampsia, it seems that animal experimentation is of little value in determining the etiology of eclampsia.

Several reports indicate that there is no abnormal renal physiology in eclampsia—pre-eclampsia. This is difficult to believe, especially since all the studies were made when the patients were secreting urine and not during the anuric phase of the disease.

One investigator states that repeated injections of Veratrone (veratrum virides) does cause a reduction in blood pressure, but at the same time there is a marked reduction in urinary output. He concludes that the use of Veratrone is contraindicated in the treatment of pre-eclampsia—eclampsia.

Several reports have been published claiming that the injection of plasma has been of great benefit in the treatment of eclampsia. Eclampsia is such a protean disease, being readily curable if early delivery occurs, that it requires a large number of cases to properly evaluate a specific treatment.

Reports are still being published in which eclampsia is attributed to faulty diet. This seems difficult to prove and certainly in most clinics eclampsia is rare, but pre-eclampsia still occurs even in patients who have been on a reasonably adequate diet.

High spinal anesthesia, especially with the catheter technique, seems of proved value in the treatment of the cardiac failure with pulmonary edema that is such a serious complication of eclampsia. If this work is confirmed, it is the most important contribution to the treatment of eclampsia—pre-eclampsia that has been developed in the past decade.

Since eclampsia—pre-eclampsia is an entity peculiar to the human race, studies as to the etiology and treatment must be made on pregnant patients and not on animals.

W. J. D.

Necrology

FRANK FARROW SIMPSON, long associated as gynecologist with the hospitals of Pittsburgh, Pennsylvania, died on Feb. 10, 1948, in Honolulu, T.H., where he resided since his retirement about twenty years ago. He was born in 1868, graduated with a baccalaureate degree from the University of South Carolina in 1889, and received his M.D. at the University of Pennsylvania in 1893. He was President of the American Gynecological Society in 1917, Vice-President of the American Association of Obstetricians and Gynecologists in 1905, Secretary General of the Seventh International Congress for Obstetricians and Gynecologists in 1912, section chairman of the American Medical Association, in 1912, Chief of the Medical Section, Council of National Defense, 1917-1918, and Lieutenant-Colonel Medical Corps, United States Army.

Editorial

ECLAMPSIA

Several reports on the etiology of eclampsia are based on the premise that the disease is primarily a hypertension due to spasm of the arterioles. Most investigators, however, believe that eclampsia—pre-eclampsia is a clinical entity in which there is first a water and salt retention due to an abnormal capillary permeability. Some of the patients develop hypertension (which may be compensatory), proteinuria, and a very few have various other symptoms and signs due to cerebral anemia, culminating in convulsions and coma.

Grollman stated that if the Goldblatt clamp is properly placed on the renal artery there is no increase in the blood pressure during pregnancy, or if there is a hypertension before pregnancy, that the blood pressure decreases to normal. The acute toxemia described by some investigators as a result of constricting the renal artery is due to too great a constriction. He thinks that the normal blood pressure is due to the increased vascular bed resulting from the pregnancy.

Smith and Smith still believe that a deficiency of estrogen and progesterone, as well as abnormal oxidation of the estrogens is associated with certain pathologic changes in the placental syncytium resulting in a failure of the latter to utilize chorionic gonadotropin. The result of this abnormal hormone and placental metabolism is the production of a protein similar to menstrual toxin. This toxin according to them is the cause of pre-eclampsia. They have treated a small group of patients with a protective pseudoglobulin which they think has resulted in clinical improvement. It is difficult for one to see any striking effects of this neutralizing protein fraction.

Grollman states that hyperfunction of the posterior lobe or the basophilic cells has no connection with the etiology of eclampsia or hypertension. He also states that it remains to be proved that hormonal aberration is the cause of toxemia and not the result of some fundamental process.

Several investigators have reported the production of the periportal hemorrhage and necrosis in experimental animals by various procedures. Dieckmann has observed several patients who showed no evidence of eclampsia prior to death, yet the liver showed the typical lesion of eclampsia. He believes that the periportal hemorrhages found in the liver are peculiar to the pregnant woman under certain conditions, but are not pathognomonic of eclampsia. A recent report indicates that thickening of the basement membrane is not always present in eclamptic patients. Thus there is no pathologic lesion either in the liver or the kidney characteristic of eclampsia.

The essayists concluded that it was impossible to influence the pituitary gland of 27 white female infantile rats with small doses of x-ray, 2 to 45 roentgen units; and, in such cases, the ovaries could not be stimulated. The anatomic findings confirmed the biological studies. Dissection and histologic investigations did not show any special difference between the experimental and 12 control animals. Increased function of the pituitary could not be observed biologically or by morphologic changes.

The eight rats treated with 50 to 1,000 roentgen units, or their eight controls, did not reveal any irregularities of ovarian function nor histologic changes of ovaries or pituitary glands.

C. E. FOLSOME.

Gynecology

Matus, V., and Moreno, G. M.: Importance of Puncture of Cul-de-Sac of Douglas in Gynecology, *Bol. Soc. chilena de obst. y ginec.* 11: 23-27, 1946.

During the years 1944-45, pelvic puncture was employed 111 times. The indications were as follows: tubal pregnancy, 50; pelvic abscess, 35; postoperative complications, 8; peritonitis, 6; no diagnosis (blank puncture), 5; tuboovarian abscess, 4; infected hematocele, 1; ovarian cyst, 1; and ruptured bladder, 1.

The authors believe that pelvic puncture is a very helpful procedure. They compare its usefulness with three other procedures used in gynecology, namely, the Schilling hennogram, endometrial biopsy, and the Friedman pregnancy test.

J. P. GREENHILL.

de Moraes, A., and do Amaral, C.: Concerning Cases of Tuberculosis of the Female Genitalia, *An. brasil de ginec.* 22: 255-262, 1946.

During the last two years, the authors observed eight cases of tuberculosis of the female genitalia among 954 patients operated on at the Gynecological Clinic of the National Faculty of Medicine of the University of Brazil. This represents an incidence of 0.84 per cent. The authors discuss the diagnosis of this condition and they particularly emphasize the importance of making microscopic examinations of all tissue removed at operation.

Gynecologic Operations

Brindeau, A., Lantuejoul, P., and Hubert, L.: The Use of Ovarian Membranes in Creation of an Artificial Vagina, *Gynec. et obst.* 45: 417, 1946.

A third successful creation of an artificial vagina, by a technique published by Brindeau in 1938, is recounted. With a sound in the bladder, and a guiding finger in the rectum, a channel is created through the perineum, between whatever labial structures are present. This channel is then lined with ovarian membranes obtained at a simultaneous cesarean section. The membrane sac is anchored to the vault with a few sutures, and the free edges are united with the margins of the original U-shaped perineal skin incision. The lined canal thus produced is packed for a week with gauze soaked with horse serum, and for a second week with gauze soaked in cod liver oil. Thereafter the patient inserts a No. 20 Hegar bougie daily for six weeks to prevent stenosis during the healing process. The membranes are gradually replaced by epithelium, and the patient reported had a good functional result. The authors have done preliminary laparotomies in these cases.

IRVING L. FRANK.

Judd, George E.: Preservation of the Upper Pelvic Floor and Bladder Support in Total Hysterectomy, *West. J. Surg.* 55: 209, 1947.

A historical review of total hysterectomy is presented. The chief support of the uterus is the endopelvic fascia which covers the pelvic organs below the visceral peritoneum. In some cases the fascia is strengthened and forms true ligaments notably in the base of the broad ligaments; posteriorly it forms the uterosacral ligaments and anteriorly the uteropubic ligaments. Cystocele is primarily a hernia of the bladder through a break in the uteropubic fascia. Prolapse of the uterus results from laceration or stretching of the endopelvic fascia, laterally and posteriorly.

Department of Reviews and Abstracts

Selected Abstracts

Malignancies

Cantone, C.: Carcinoma of the Stump After Supravaginal Hysterectomy, *La Ginecologia* 12: 285, 1946.

During the period between 1938 and 1944, carcinoma of the stump after supravaginal hysterectomy was observed in the Department of Obstetrics and Gynecology of Vercelli in 0.67 per cent of the cases.

Mortality rate, after total hysterectomies (excluding operations performed for carcinoma), reached 2.50 per cent, while in cases of supravaginals the mortality was reduced to 1.38 per cent. The number of total hysterectomies during the above-mentioned years was 182, the number of subtotal hysterectomies 595.

Cantone recalls the opinion of some gynecologists in this country, that in hospitals where hysterectomies are not very frequently performed, the supravaginal operation should be considered the method of choice, if a definite indication for a total hysterectomy is not present, but believes that the matter requires further investigation. GEMMA BARZILAI.

Furth, J., and Sobel, H.: Hypervolemia Secondary to Grafted Granulosa-Cell Tumor, *J. Nat. Cancer Inst.* 7: 103, 1946.

Hypervolemia (increased blood volume) occurs in mice engrafted with certain, but not all, strains of granulosa cell tumor. It amounts to over twice the average volume found in normal animals, or in mice bearing other tumors. There is an increase in plasma volume (in contrast with human polycythemia), a twofold increase in total red cells, and in cells per unit weight; and a slight fall in red-cell count and in hematocrit. At necropsy there is marked congestion of liver, spleen, adrenals, and bone-marrow. The hypervolemia does not parallel the tumor size, the amount of organ congestion, nor the extent of estrogenic change. It does not follow massive doses of estrogens alone.

These tumors evidently produce a substance which affects the blood volume mechanism, and cause the appearance of blood changes like those seen in pregnancy. The substance may be a hormone like those secreted by the adrenal cortex. IRVING L. FRANK.

Endocrinology

Baidins, Von A., Claesson, L., and Westman, A.: On the Influence of Roentgen Treatment Upon the Gonadotrophic Function of the Pituitary, *Gynaecologia* 122: 347-362, 1946.

The authors, reporting from the Woman's Clinic of Karolinska, Stockholm, attempted to re-evaluate the gonadotrophic function of the pituitary gland after x-ray treatment. In their opinions this problem was unsolved. The authors, therefore, investigated the influence of x-rays upon the gonadotrophic function of immature female white rats, using 61 animals of which 38 were in their study groups and 23 were employed as controls.

Mustakallio, M. J.: On Congenital Sincipital Encephalocele and Its Treatment, With Special Reference to the Structure of the Wall, *Ann. Chirurg. et Gynec. Fenniae* 35: Supplement 2, 1946.

A monograph on the subject of congenital encephaloceles is presented. The literature on the subject, going back as far as the early part of the eighteenth century is covered in detail. Four cases of sincipital encephalocele, all of which were operated and all of which recovered, are then reported. Two were female infants; one three weeks old, and the other seven months old. The other two were a male of 17 years and a female 20 years of age. The symptoms, differential diagnosis, prognosis, and treatment of the condition are then discussed. It is stated that Dandy felt that operation should be postponed until the infant was one year old. However, the results shown by the author in the two infants operated would tend to contradict this.

A detailed study was made of the tissue removed from three of the four cases and anyone interested in this subject would be well advised to refer to this section of the monograph. Finally, in discussing the etiology the author states that, inasmuch as there have been several reports of two or even three cases in the same family, "we must assume that some endogenic factor does exist."

HERBERT J. SIMON.

Nelson, T. Y.: Intracranial Damage in the Newly Born, *M. J. Australia* 1: 268, 1947.

The author wishes to stress the group of cases in which the intracranial damage is so great and the symptoms are so severe that the question of survival is in doubt. The subdural type of hemorrhage is the most frequent and the intracerebral the most infrequent. The various signs and symptoms referable to the different types of intracranial hemorrhage are described. A detailed description of subdural hemorrhage is given as well as means of substantiating this diagnosis.

Early diagnosis and appropriate treatment are essential if the baby is to survive. The author feels that if the presence of blood in the subdural space can be established, the blood should be evacuated as early and as completely as possible.

WILLIAM BERMAN.

Maternal Vitamin A Intake and Ocular Abnormalities in the Offspring,* *Nutrition Rev.* 5: 89, 1947.

The eyes of young, born of rats unmarkedly deficient in vitamin A, show a variety of major anatomic defects and distortions. For these to appear, the maternal serum vitamin A must be one-tenth normal or less; a level at which 25 per cent of the mothers die, fetal resorption is common, and normal birth impossible. At slightly higher levels the eyes show no change whatever. Therefore, it is reasoned that congenital retrolental fibroplasia, which occurs in 8 per cent of infants weighing less than 5 pounds at birth, is probably unrelated to vitamin A deficiency.

IRVING L. FRANK.

Fukas, Von M.: Streptococcic Sepsis of the Newborn From Mastitis in the Pregnant Mother, *Gynaecologia* 123: 53-57, 1947.

Fukas, of Athens, reports an unusual case where a normal male infant was delivered without maternal complications. The baby was apparently in excellent health until three days of age, and ultimately died of streptococcal septicemia. Autopsy confirmed the diagnosis. The mother had suffered from serious mastitis of the left breast for two months prior to delivery. The author was of the opinion that the portal of entrance to the baby was via hematogenous transmission of streptococci in utero, and that the spread of infection occurred in the baby when the antibodies from the mother had been overcome by the overwhelming infection. The placenta was negative to histologic study.

C. E. FOLSOME.

*This is a review article, based on papers of:

1. Warnaky, J., and Schraffenberger, E.: *Proc. Soc. Exper. Biol. & Med.* 57: 49, 1944.
2. Jackson, B., and Kinsey, V. E.: *Am. J. Ophth.* 29: 1234, 1946.

The author describes and illustrates his technique for total hysterectomy based on the above anatomie knowledge. The broad ligaments are cut and ligated, and the uterine vessels ligated and cut. A cuff of the endopelvie faseia is then made by a circular incision around the cervix. The anterior cuff is pushed down along with the bladder; the posterior is pushed along with the uterosaeral ligaments, and the lateral or cardinal ligaments are dissected free of the uterus and ligated. The vagina is entered posteriorly, and a circular incision made to remove the uterus. Sulfanilamide powder is put in the vagina. The vaginal cuff is closed and then the faseial cuff, including the cardinal ligaments laterally and the uterosaeral ligaments posteriorly, is sutured over the vaginal vault. Where a cystocele exists the uteropubic faseia is approximated to provide a new floor for the bladder. The entire area is peritonealized by suturing over with the peritoneal fold of the bladder.

WILLIAM BICKERS.

Menopause

Taylor, R. D., Corcoran, A. C., and Page, Irvine H.: Menopausal Hypertension: A Critical Study, *Am. J. M. Sc.* 213: 475-476, 1947.

The authors, reporting from the Lilley Laboratory for Clinical Research, Indianapolis City Hospital, followed 179 castrated women and twenty-one with the natural menopause. They demonstrated, in these cases, that arterial hypertension was no more common in them than in the general population. "Vasomotor instability," as exhibited by "hot flashes," perspiration, and tachycardia were not necessarily associated with hypertension, and their alleviation by estrogens need not affect arterial pressure.

The menopause seemed to intensify pre-existing psychonouroses. Despite severe neurotic behavior, hypertension did not develop within three or more years except in six of those 200 subjects. From these data the authors conclude that the relationship of the menopause and hypertension was incidental, and the loss of ovarian secretion was neither a primary nor a contributory cause of arterial hypertension.

C. E. FOLSOME.

Newborn

Rossi, Antonio: Weight and Length of Newborn, *Ginecologia* 12: 100, 1946.

Rossi reviews weight and length of newborn babies, and the weight of the placenta, of confinement cases in Novara, Italy, from 1937 to 1943. A definite decrease in weight, length of the babies, as well as a reduction in the weight of the placenta is noted. This applies to the population as a whole, as well as to different social and financial groups: housewives, factory workers, women from rural districts.

The average weight of the newborn babies for the entire population in 1937 amounted to 3,236 Gm., and in 1943 it decreased to 3,030.8 Gm. The average length of the newborn was 50 cm. in 1937, and decreased to 49.5 in 1943. The weight of the placenta was 547 Gm. in 1937, and 526 Gm. in 1943. On considering weight differences in the various social groups, one finds in the group of babies of housewives a decrease from 3,330.9 Gm. to 3,063.5 Gm. in weight; 50.3 cm. in 1937 to 49.7 cm. in 1943 in length; and a decrease in placenta weight from 552 Gm. to 521 Gm. In the factory workers, the most underprivileged group in Italy, the weight of the newborn babies reached a low of 2,955.6 Gm. in 1943, as compared with 3,142.5 Gm. in 1937. The length of the babies showed a decrease from 49.6 cm. to 49.2 cm., and the weight of the placenta was reduced to 517 Gm., as compared with the average weight of 541 Gm. in 1937. In the rural districts, the decrease was less spectacular. From an average weight of 3,197 Gm. in 1937, there was a drop to an average of 3,077 Gm. in 1943. From a length of 50 cm., there was a decrease to 49.6 cm., and the weight of the placenta decreased to 528 Gm. from the average 538 Gm. in 1937.

Conclusion: A definite reduction of the length and weight of the fetus, and of the weight of the placenta, which—although showing some differences in favor of the babies of women in rural districts, and a maximum drop in the group of factory workers—is equally noted in the population as a whole, and must therefore be credited to the deterioration of nutrition and emotional strains associated with war.

GEMMA BARZILAI.

Correspondence

Induction of Labor

To the Editor:

I have read with great interest the report of the discussion on the induction of labor which took place at the Chicago Gynecological Society in November, 1946, and was published in the *JOURNAL* in September, 1947 (p. 496).

Most British obstetricians will agree with the general conclusions therein, but there is one comment I should like to make on the methods advocated for inducing premature labor.

As Dieckmann and McCready state in their article, the Drew-Smythe catheter is used extensively in British hospitals, and indeed it is the almost universal method of choice. Bags, bougies, etc., are now rarely used, and many of us in this country have long been surprised at the retention of these cumbersome and dangerous instruments by American obstetricians. The reluctance to adopt the catheter method is also curiously conservative. This method carries the great advantage of leaving the forewaters, and consequently the uterine bacteriologic barrier, intact, and has drastically reduced the incidence of infection. As Dieckmann says, labor does not ensue immediately in all, but it does in the great majority of cases, and in any event the procedure may be repeated twice, or even three times.

Simultaneous stimulation with a complete medical induction is a useful reinforcement, and the danger of hemorrhage from damage to the placenta is negligible in careful hands.

ALBERT DAVIS.

93 HARLEY STREET,
LONDON, DEC. 31, 1947.

Drainage of a Hydrocephalic Head

To the Editor:

D. N. Danforth (*AM. J. OBST. & GYNEC.* 54: 694-695, 1947) presents a modification of the procedure mentioned by Stander for decompressing and draining a hydrocephalic head in a breech presentation. Still another slight modification, available when the spinal canal is opened in the cervical region, consists in using a metallic catheter for passage into the distended ventricles. This variation permits easy collection of the fluids, so that it may be measured for the record.

When there is a spina bifida, as so often happens, a metallic or stiff silk catheter, depending upon the location of the defect, may be passed through the defect in the vertebral arches. Moreover, when the hydrocephalic head presents by the vertex, its fluid contents may be easily drained through a regular abdominal paracentesis trocar passed through an open suture under sight or touch.

These procedures have been employed for many years and have greatly simplified the management of labor complicated by cephalopelvic disproportion on the basis of hydrocephalus, but are rarely mentioned in standard textbooks. They are so much simpler than the classic techniques that their general adoption would seem indicated.

E. D. PLASS, M.D.

IOWA CITY, IOWA
Nov. 3, 1947

Pregnancy

Belvederi and Morano: Ophthalmoscopy Study of the Eyeground in Pregnancy, *Riv. ital. di ginec.* 28: 3, 1945.

Belvederi and Morano of the Medical School of Bologna studied retina changes in 142 cases of normal and impaired pregnancies. They found venous hyperemia, retinal vessel spasm, retinal edema, and cottonwool exudate, hemorrhages, macular stars, detachment of the retina, and amaurosis.

They discuss the relationship of those ocular signs and symptoms to findings in cases of pregnancy showing no other pathologic change, in cases associated with renal diseases, or associated with toxic changes.

In cases of otherwise normal pregnancy, venous hyperemia was present in 36 per cent, retinal spasm in 38 per cent, edema in 30 per cent, and retinal stars in 4 per cent of the cases.

In pre-eclampsia, 22 per cent of the cases showed normal eyegrounds; 44 per cent showed venous hyperemia; 38 per cent, retinal spasm; 51 per cent, retinal edema; 15 per cent, retinal stars; 9 per cent hemorrhages; 2 per cent, detachment of the retina.

In cases of renal disease in pregnancy, the eyeground was normal in 37 per cent, there was venous hyperemia in 62 per cent of the cases. Retinal arterial spasm was present in 25 per cent of the cases, retinal edema in 50 per cent, retinal stars in 37 per cent, retinal hemorrhages in 12 per cent.

In cases with severe eclampsia, the eyeground was normal only in 15 per cent of the cases, venous hyperemia was present in 47 per cent, arterial spasm in 43 per cent, retinal edema in 75 per cent, outlined macular stars in 43 per cent, retinal hemorrhages in 34 per cent, detachment of the retina in 6 per cent, amaurosis in 9 per cent of the cases.

On the basis of their findings, the authors advocate routine eyeground examinations on all pregnant women, and repeated examinations in all cases associated with more or less obvious symptoms of toxic changes, or of renal diseases.

GEMMA BARZILAI.

Gianaroli, L.: Capillary Fragility in Pregnancy, *Riv. ital. di ginec.* 28: 225, 1945.

Studies conducted during wartime by Gianaroli on women at various stages of gestation indicate that a latent vitamin C deficiency was present throughout among pregnant women in the obstetric department of the Medical School in Bologna.

Vitamin C deficiency was evaluated indirectly by approaching capillary fragility. This was done by Cianci's method, that consists in counting the petechiae appearing at bend of elbow, following the application of a suction bell.

During pregnancy and during puerperium, abnormal capillary fragility was demonstrated. It was, however, readily lowered by oral supply of 200 mg. vitamin C daily for seven consecutive days, while a much higher dose was requested to reduce capillary fragility during the puerperium. This shows that in the puerperium there was a higher degree of vitamin C reserve deficiency.

The result of this evaluation of latent vitamin C deficiency through demonstration of capillary fragility parallels findings by Maciotta in earlier research in the same medical school in which vitamin C content of blood and urine was measured in different stages of gestation.

GEMMA BARZILAI.

Toxemia

Umberto, Bracale: Blood and Bone Marrow Disorders Associated With Eclampsia, *Arch. di obstet. e ginec.* 51: 245, 1947.

In a series of 21 pregnant women, with eclampsia, blood and bone marrow elements were studied. In the peripheral blood, erythrocytes, hemoglobin, and lymphocytes appeared reduced in number, while leucocytes were numerically increased.

In the bone marrow that was obtained by puncture of the sternum, anisocytosis, microcytosis, and macrocytosis were present in the elements of the red series. Hemohistioblasts were increased, and the red and white cell index shifted toward the latter. Myelocytes were definitely increased. As a whole the blood picture revealed alterations in both red and white elements.

GEMMA BARZILAI.

Items

American Board of Obstetrics and Gynecology, Inc.

Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted in Washington, D. C., by the American Board of Obstetrics and Gynecology from Sunday, May 16, through Saturday, May 22, 1948. The Shoreham Hotel in Washington will be the headquarters. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Shoreham Hotel.

Candidates for re-examination in Part II must make written application to the Secretary's Office not later than April 1, 1948.

Candidates in military service are requested to keep the Secretary's Office informed of any change in address.

Applications are now being and will be received until November 1, 1948, for the 1949 examinations. For further information and application blanks, address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.
Secretary.

Notice to Diplomates

American Board of Obstetrics and Gynecology, Inc.

The forthcoming fourth edition of the Directory of Medical Specialists plans to designate by appropriate abbreviations whether Diplomates of the above Board practice both branches of the specialty or major in one or the other. The letters OG will be used to indicate combination of practice in both branches, the letter O that the Diplomate majors in obstetrics, and the letter G that he majors in gynecology.

Diplomates who have not already notified the Directory Publication office on this matter in making their biographic returns should communicate with the Directory of Medical Specialists, 210 East Ohio Street, Chicago, Illinois.

PAUL TITUS, M.D.
Secretary.

Erratum

In the article by Lois A. Day, Robert D. Mussey, and Robert W. DeVoe, entitled "The Intrauterine Pack in the Management of Postpartum Hemorrhage," in the February issue of the JOURNAL, on page 234, in the third line above Table II, "276 patients" should read, "267 patients."

Screw Type Cervical Cannula

To the Editor:

I have read, with much interest, the letter of Dr. Paul Titus which appeared in your June (1947) issue; also, the discussion in the November issue.

As one who, for a number of years, has been especially interested in the screw-thread-tip cannula, I was greatly interested in Dr. Titus' remarks, advising against its use.

I should like, very much, to know whether this opinion is based upon theoretical considerations—or whether Dr. Titus has actually had unfavorable experiences with this type of cannula.

I ask this question because I have used this type of cannula over a period of many years and have followed through the results—not only following the examination but also after delivery; this observation covering a number of years. To date, I have not found any unfavorable results from the use of this instrument. Neither have I had one report of any specific case of injury or disturbance following its use.

If, however, definite cases of injury have been observed, they should be specifically and scientifically reported. It is for this reason that I ask the definite question.

I receive frequent requests for information concerning this technique, and I should like to be specific and accurate in my replies.

The observations and experiences of Dr. Titus—and of others who have used this technique—would be greatly appreciated.

A. P. HUDGINS, M.D.

CHARLESTON, W. VA.
Dec. 6, 1947

Hysterosalpingography—Reply by Dr. Bickers

To the Editor:

The discussion relative to the various procedures in current use relative to "Hysterosalpingography" which appeared in the February, June, and November, 1947, issues of your journal has aroused my interest. Specifically I am concerned over the reference of Dr. Titus and Dr. Weisman to the trauma which they have observed incident to the use of the screw type cannula. This instrument, which was introduced several years ago by Dr. A. P. Hudgins, has so greatly facilitated and expedited hysterosalpingography as an office procedure that I am among those who feel that the instrument has real merit, and its place in the study of human sterility is an important one.

The screw type cervical cannula has been used by me for 112 hysterosalpingographys on 104 patients. In each case the cannula was removed immediately after the x-ray study was completed, and in no case was there any bleeding following the removal. This would seem to indicate that there was little trauma associated with its use. Indeed, it is my impression that this instrument produces less trauma than the tenaculum which is necessary when one uses the conventional type of cannula. In checking the records on these patients hurriedly I have not been impressed with any increased incidence of cervical erosion nor chronic endocervicitis following the use of this cannula. The ease with which it can be used, the minimum discomfort to the patient, the vastly improved uterine filling and the complete absence of any evidence of trauma to the cervix would seem to permit unqualified recommendation of its use.

WILLIAM BICKERS, M.D.

RICHMOND, VA.
Dec. 28, 1947

physiologic basis for the development of the Graafian follicles and ovulation, suggests that the ovum, or a "system of self-contained organizers," may have a guiding influence in this process. This concept of ovarian stromal cell multipotentiality is in accord with the view of the totipotentiality of the mesenchyma in the urogenital ridge (Schiller,⁸ Gräfenwald⁹). In connection with the multiplicity of function, interesting histochemical evidence is advanced by Dempsey and Bassett.¹⁰ They found that the cells of the theca interna and corpus luteum contained sterols, while the granulosa cells did not.

The Interstitial Cells of the Ovary.—In 1865 His¹¹ described aggregates of lipid-laden epithelioid cells in the ovaries of cats. In 1901 and 1902 Limon¹² and Bouin¹³ considered these as endocrine gland-cells and proposed the term "interstitial gland of the ovary." Other investigators, notably Wallart,¹⁴ agreed with these observations and in 1907 the latter author, studying human material, found the incidence of interstitial cells to be highest at puberty. Kingsbury,⁵ in 1914, thoroughly reviewed the subject and studied the problem in the ovary of the cat. In 1919 Corner,⁶ investigating the development of the corpus luteum in the sow, made observations on the ovarian stroma in this animal as well. It is now generally held that the interstitial cells are remnants of granulosa from atretic follicles and that subsequent contraction of the scar may displace the cells well away from the original site. Kingsbury⁵ was of the opinion that there is no morphologic or physiologic support for the idea of an interstitial gland of the ovary per se.

Recent knowledge about the structure and hormonal effects of the granulosa and theca cell tumors (Novak,¹⁵ Dockerty¹⁶) supports, in our opinion, the original views of Limon, Bouin, and Wallart, at least as to the hormonal potentiality of the interstitial cells. Several points of caution in the study of this problem are in order. In the past, most of the material used was from animals in the very young or fertile period of life. Very little human material was examined and the knowledge of the senile ovary, in particular, is very scant. True, it is important to distinguish the interstitial cells from aggregates of granulosa cells which only on serial section can be shown to be part of a maturing or atretic follicle. Similarly, in senility, small groups of invaginated germinal epithelium may also simulate interstitial cells. Nevertheless, our study leads to the conclusion that, at least in the senile ovary, the stromal cell is capable of recapitulating the normal sequences of the granulosa, theca interna, corpus luteum, and their neoplastic derivatives without the presence of the primordial ovum. We have seen numerous instances of this process in its various transitional stages, without relation to atretic follicles or their scars.

The Ovary in Endometrial Carcinoma.—Advances in the knowledge of hormonal factors in cancer have been associated with studies on the relation of the granulosa and theca cell tumors to endometrial carcinoma (Novak,¹⁵ Dockerty¹⁶). The association of endometrial hyperplasia with carcinoma was first investigated by Taylor,¹⁷ and then Herrell,¹⁸ and Novak.¹⁹ The endocrinological aspect of uterine cancer in general is ably reviewed by Dockerty,¹⁶ Block,²⁰ and Nathanson.²¹ Jones and Brewer²² reported on a study of the uterus and ovaries in 67 cases of fundal cancer. They concluded that there is no relation between ovarian "cysts," endometrial hyperplasia, and endometrial carcinoma. Of the total series, none of the patients was over 51 years of age. There were only five patients in the 45 to 51 year age group. The conclusions are based mainly on the premenopausal group. Corpora lutea are described with an inner fibrous lining, yet no comment is made about the condition of the lutein cells. This lining is seen best in the retrogression stage. In our series there were corpora lutea which we considered definitely abnormal in that while the fibrosis at the inner and outer borders was well advanced, the lutein cells and their capillary

American Journal of Obstetrics and Gynecology

VOL. 56

OCTOBER, 1948

No. 4

Original Communications

THE OVARY IN ENDOMETRIAL CARCINOMA

With Notes on the Morphological History of the Aging Ovary

EPHRAIM WOLL, M.D., ARTHUR T. HERTIG, M.D., GEORGE VAN S. SMITH, M.D.,
AND LENT C. JOHNSON, M.D., BOSTON, MASS.

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IN 1941, one of us (G. Van S. S.),¹ in a study of 307 consecutive cases of carcinoma of the endometrium, noted that in 156 (87 per cent) of 180 menopausal cases, there was a stromal hyperplasia of the ovaries. In 1942, another of our group (L. C. J.),² then at the Free Hospital for Women, amplified that observation and gave a preliminary report before the New England Pathological Society. This finding aroused considerable interest and initiated a study of the aging ovary in general. A note on this subject was made by one of the writers (A. T. H.).³ The earliest appearance of stromal hyperplasia was seen in the 45 to 49 year age group. After the age of 50 years it was seen with greatest frequency in cases with continued endometrial activity or outright malignancy. On the basis of these observations the present study was undertaken (1) to learn the stromal changes in the ovary from neonatal infancy to old age; (2) to study the ovaries in cases of carcinoma of the endometrium; (3) to compare these with a control group.

Review of Literature

The Ovarian Stroma Before the Menopause.—The normal sequences of the stromal cell are at present considered to be as follows (Fischel,⁴ Kingsbury,⁵ Corner⁶): in the embryo the local mesenchyme gives rise to the stromal cell which in postnatal life is modified to become the cell of the granulosa, theca interna, corpus luteum, and finally the corpus albicans. For the purposes of this paper we wish to emphasize the following features of the above enumerated sequences. The spindle-shaped stromal cell gradually grows larger, becomes cuboid, shows accumulation of anisotropic fat, and then in retrogression degenerates and is replaced with scar tissue.

The stromal cell has thus a multipotentiality of form and probably function which normally follows an orderly sequence. Hisaw,⁷ in his review of the

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Fibroblasts actively proliferate at the outer margins, the inner border, and between the clefts, but never invade the reticular bed of the degenerated granulosa lutein cells. Ultimately the reticulum is hyalinized into a homogeneous mass of rather special scar tissue. The vascular bed atrophies, the corpus albicans is sharply demarcated from its surrounding structures and, albeit vaguely, retains the outlines of its precursor.

In the formation of an atretic follicle the sequences are essentially similar to those resulting in the corpus albicans, except that there is more fibrous penetration. A band of material similar to the hyalinized reticulum of the corpus albicans, but much narrower, remains. Occasionally a few small round pyknotic cells, possibly remnants of granulosa or theca cells and a few lymphocytes are seen in and around the scar.

It is readily agreed that with ordinary staining methods the individual resting stromal cell is indistinguishable from a fibrocyte, but from the following evidence we conclude that the stromal cell is at least a special type of connective tissue and that it does not produce collagen in the usual sense. (1) The resting stromal cells *en masse* are recognized through most of the life of the ovary by the relative lack of collagen and the presence of delicate intercellular reticular fibrils. These usually have no constant orientation in respect to the axis of the nucleus. Collagen fibers, in contrast, are usually in the direction of the long axis of the nucleus. This is seen best in the Foote's reticulum stain counterstained with Van Gieson. (2) Very early in embryonic life the tunica albuginea is distinguished from the rest of the cortex by an abundance of collagen. In senescence it becomes the main source for fibrosis of the ovarian stroma. (3) A study of the young corpus luteum with reticulum and connective tissue stains makes it possible, we believe, to differentiate the theca lutein cells from the fibroblasts. (4) The formation of a corpus albicans resembles but is not identical with scar tissue formation elsewhere in the body. That the stromal cell is normally in intimate relation with fibrous tissue is not disputed. The remarkably rich capillary network in the cortex with its adventitial fibroblasts makes this point quite clear. The thecoma (Fig. 1) recapitulates and even exaggerates this fundamental pattern very well.

Ovarian Stroma in Senescence and Senility.—The description by Hertig² need not be repeated here except to emphasize the stromal changes. In senescence there is a gradual disappearance of the primordial ova, Graafian follicles, maturing or atretic, and follicular cysts. Aside from the "germinal" inclusion type and its derivatives, cysts are extremely rare after 50 years of age. In senility the stromal cell nuclei shrink greatly. Fibrous tissue penetrates the cortical stromal layer from the tunica albuginea as well as from the medulla. The reticular fibrils become hyalinized. Additional collagen is derived from the vascular adventitia. Finally, in advanced old age, the cortex is distinguishable with difficulty from old fibrous tissue elsewhere in the body (Fig. 2). From the age of 40 years on the incidence of germinal inclusion cysts increases. These must be differentiated from the follicular, theca lutein, or corpus luteum types. In the latter at least, the remnants of a theca interna and its vascular wreath can often be recognized. To speak of "cysts" without qualification adds to the confusion. The so-called "simple cyst," as the term is used in this laboratory, is a structure of unknown antecedents. It may be of follicular or germinal epithelial origin, but the lack of definitive epithelium makes it impossible to determine which structure is responsible for cyst formation.

In the senile ovary there is considerable individual variation in the amount of residual stroma and the number and size of corpora albicantia. This is probably, at least in part, a reflection of the individual's past history (frequency of ovulation, atresia of follicles, intra-abdominal, and systemic disease).

bed were remarkably well preserved and apparently functionally quite active. This subinvolution, and presumable persistence of hormonal stimulation, we consider to be significant. It is of particular interest to us to note that Jones and Brewer speak of a "dense" stroma in their cases, and that a photograph in Herrell's report to illustrate a typical "cystic" ovary encountered frequently in his series shows several dark areas in the stroma.

Materials and Methods

All the cases of endometrial carcinoma from the files of the Free Hospital for Women, in which sections of the uterus and ovaries were available, were used. A small number was excluded because (1) the diagnosis of carcinoma was not clear-cut; (2) the sections were faded; (3) the ovarian architecture was markedly distorted by metastatic or associated primary tumor; (4) the sample chosen (only the wall of a cyst, for example) did not permit valid observations of the ovary. A total of 331 acceptable cases were examined. The tissue was fixed in formaldehyde, 10 per cent, U.S.P. or Bouin's fluid, embedded in celloidin or paraffin, and stained with hematoxylin and eosin. In several instances, the sections were also stained with Mallory's aniline blue, phosphotungstic acid hematoxylin, and Foote's reticulum, counterstained with Van Gieson.

For the control group, an approximately equal number of cases, with the same age distribution, was chosen from the autopsy files of the Peter Bent Brigham Hospital. The same criteria as above were applied. In order to approach the normal as much as possible, preference was given to cases of cerebral hemorrhage, coronary occlusion, fulminating sepsis, or sudden death from other causes. A total of 307 such cases was examined. In none was there clinically appreciable gynecologic disease. The tissue was fixed in Zenker's-acetic acid or formalin, embedded in paraffin, and stained with eosin-methylene blue or hematoxylin-eosin.

To evaluate differences in microscopic appearance due to differences in preparation methods, sections of the ovary from ten cases of endometrial carcinoma, prepared as the rest of the control group, were studied but not included in the tumor series. Although Zenker's-acetic acid fixative does accentuate collagen and produces more nuclear shrinkage than Bouin's fluid, the differences were judged not sufficient to make comparisons unreliable.

In addition, numerous sections from the ovaries of the newborn, infants, children, and adolescents from the autopsy files of the Children's Hospital were prepared with all the above enumerated fixation and staining techniques, except celloidin, and were studied to obtain an understanding of the morphologic history of the ovary, especially its stroma. In this group, too, an attempt was made to choose cases of sudden death, brain tumor, birth injury, etc. In almost all cases, the tumor, control, and study groups, the ovarian sections represented a mid-coronal plane and were, therefore, anatomically comparable.

Results and Analysis

Ovarian Stroma Before the Menopause.—It is generally held that the ovarian stromal cell has the potentiality to act as a fibroblast as seen in the atretic follicle, the corpus albicans, or in ovarian neoplasms such as the fibroma, granulosa, and theca cell tumors. Our observations lead us to conclude that this cell, in its behavior as a connective tissue element and the true fibroblast, are not identical. The morphologic differences are first seen best when the luteinized cells of the theca interna, accompanied by capillaries, and in our opinion fibroblasts as well, penetrate between the clefts of the young corpus luteum. When the latter retrogresses the epithelial elements degenerate but leave behind a very delicate but rich reticulum. It is at first argentaphil and later stains as collagen.

the nucleus of the resting stromal cell. This pattern we consider minimal evidence of stromal hyperplasia.

In a smaller number of cases one observes a still greater increase in the width of the nucleus, condensation of the chromatin into coarse granules, and



Fig. 3.—The ovary from a 59-year-old woman, showing stromal hyperplasia. Note its nodular character. Hematoxylin and eosin, $\times 10$.



Fig. 4.—Detail of stromal hyperplasia. Note the dark appearance and the condensed connective tissue at the periphery of the nodules. E.M.B., $\times 30$.

occasionally the appearance of small poorly demarcated clear spaces in the ground substance. Many of the cells exhibit a prominent nucleolus seen best in Bouin's fixed tissue. The accompanying capillaries appear more prominent than usual (Fig. 9).

In a still smaller number of instances one sees the above picture plus scattered frankly epithelial lipid-laden cells with a round nucleus 8 to 9 mu

Ovarian Stromal Hyperplasia.—The ovary in most cases of endometrial carcinoma has a cortex which is unusually dense and often assumes the shape of spherical or scalloped masses. These do not necessarily bear a relation to the surface gyri. The pattern is reminiscent of miliary intramural leiomyomas of



Fig. 1.—Section of thecoma to illustrate fundamental pattern of ovarian stroma. The dark granules of lipid are limited to the ovarian stromal cells. The clear zones, usually around vessels, are free of lipid and contain fibrocytes and collagen. Hematoxylin-Sudan III, $\times 130$.



Fig. 2.—A senile ovary from a 69-year-old woman. A germinal epithelium inclusion cyst is also shown. E.M.B., $\times 30$.

the uterus (Figs. 3 to 6). On more detailed examination it is seen that the stromal cells are grouped into more than the usual number of whorls and fascicles (Fig. 8). The nucleus is bluntly oval instead of the usual spindle shape of the resting cell. The nucleus reaches a length of 12 to 15 μ and a width of 6 to 8 μ . The chromatin is disposed at first loosely in a clear ground substance. Subsequently it is gathered into large granules. The reticular fibrils become readily recognizable. Collagen is scant. This accounts for the naked-eye impression that the cortex is unusually dark. It is not due to hyperchromatism of the stromal cell nucleus. The latter, in fact, is lighter on the whole than

a transformation into foreign-body giant cells, or degeneration with giant cell response. This is associated with proliferation of capillaries in the early stage, and the development of intra and extra cellular crystals of anisotropic fat (Figs. 11 to 13). These are the "cortical granulomata" described by Hertig.² It is to be emphasized that the history of the patients showing such structures in their ovaries did not give any grounds to believe that these cortical granulomas were the result of foreign bodies introduced surgically or derived from known

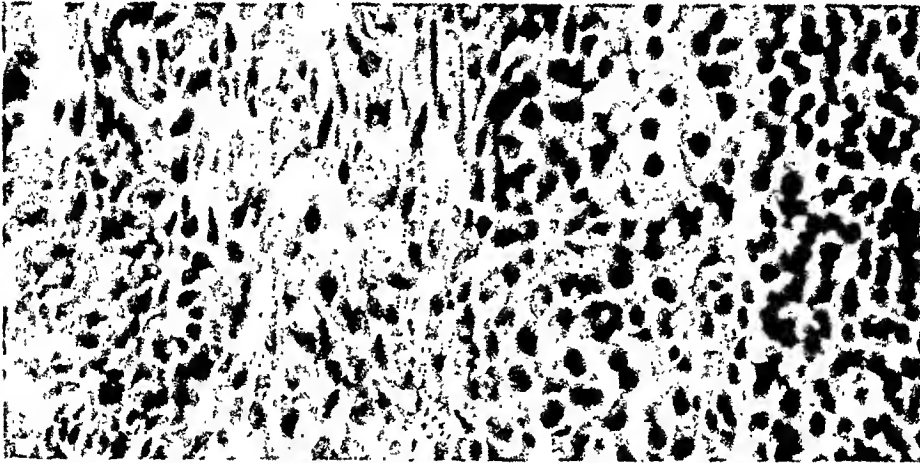


Fig. 7.—Segment of maturing Graafian follicle. The normal sequences of the stromal cell, exclusive of luteinization, are shown. Hematoxylin and eosin, $\times 540$.

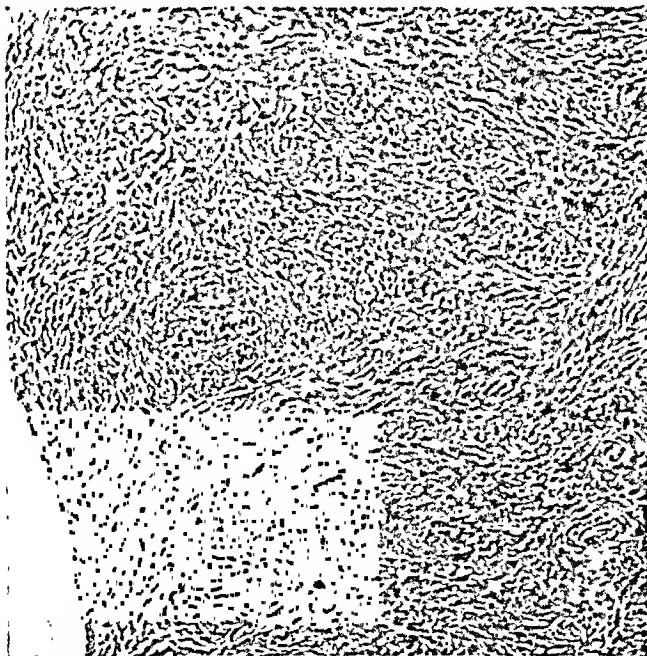


Fig. 8.—Stromal hyperplasia. Note the plumpness of the cells and increase in whorling. Hematoxylin and eosin, $\times 130$.

intraperitoneal disease. We do not know with certainty whether the epithelial cells are transformed into foreign body giant cells or whether the former degenerate and lead to giant cell response. It is of interest in this connection to note

wide containing a prominent nucleolus. The cell margin is distinct. These cells are seen singly or sometimes in groups. Transitional forms between the resting stromal cell and the above are also seen (Fig. 10). These aggregates bear no relation to atretic follicles or their scars. For this appearance we use the term thecomatosis.



Fig. 5.—A more diffuse variant of stromal hyperplasia. Hematoxylin and Eosin, $\times 10$.



Fig. 6.—Stromal hyperplasia involving part of the medulla (woman, aged 62 years, menopause at 50 years). Hematoxylin and eosin, $\times 10$.

What we believe are retrogressive changes are now to be considered. They are characterized by: (1) a reduction in the size of the nucleus; (2) increase in the amount of true collagen; (3) hyalinization of the reticular fibrils. The nodular character of the stromal hyperplasia is somewhat accentuated by a coarsening of the molded collagen around the periphery. Thus it is possible to recognize evidences of a former hyperplasia (Fig. 12).

In retrogression, at least some of the epithelial cells above described do not revert to the appearance of a resting stromal cell. Instead, there is apparently

Stromal hyperplasia was diagnosed whenever most of the cortex showed the above-described findings. Stromal hyperplasia is a generalized process. Therefore, even a small amount of available cortex in a given section may be sufficient to make the diagnosis. Because this is essentially a quantitative change, there

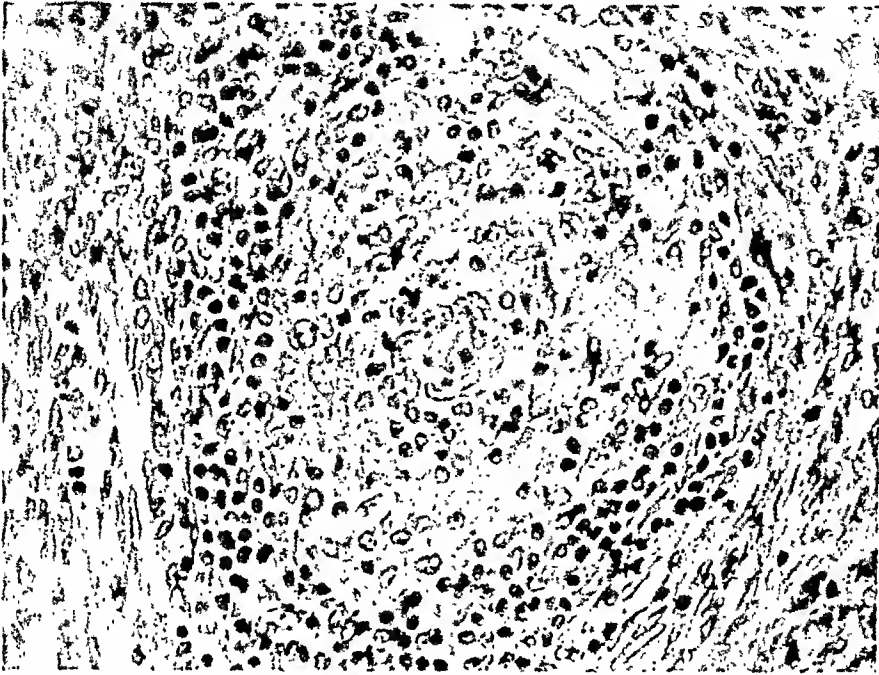


Fig. 11.—Early stage in the formation of a cortical granuloma. Hematoxylin and eosin, $\times 540$.

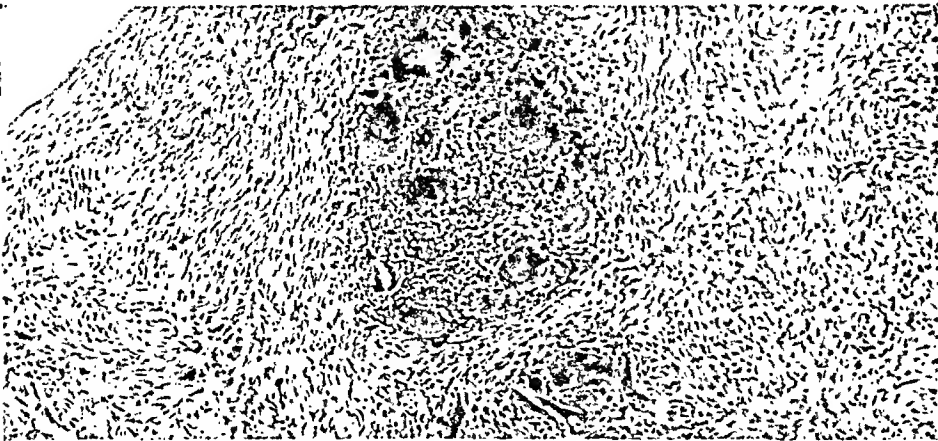


Fig. 12.—Old cortical granuloma. Note the retrogressive changes in the adjacent stroma. Hematoxylin and eosin, $\times 135$.

were not a few instances where a strictly objective decision was quite difficult. Thus the general figures are valid to indicate a trend only. Of some help was the knowledge of the patient's age. An unusually well-preserved ovarian cortex in a woman of 60 years or over weighed heavily in favor of hyperplasia, while in the woman of 35 years or less, the same appearance was not significant, unless other signs of hyperplasia were found.

Corner's⁶ observation that the lutein cells can transform themselves into macrophages. The above-described stromal changes are, in our opinion, an abnormal recapitulation of the normal sequences of the stromal cell (Fig. 7). All of these, except the cortical granulomas, are seen in the natural history of the follicle, corpus luteum, and corpus albicans.

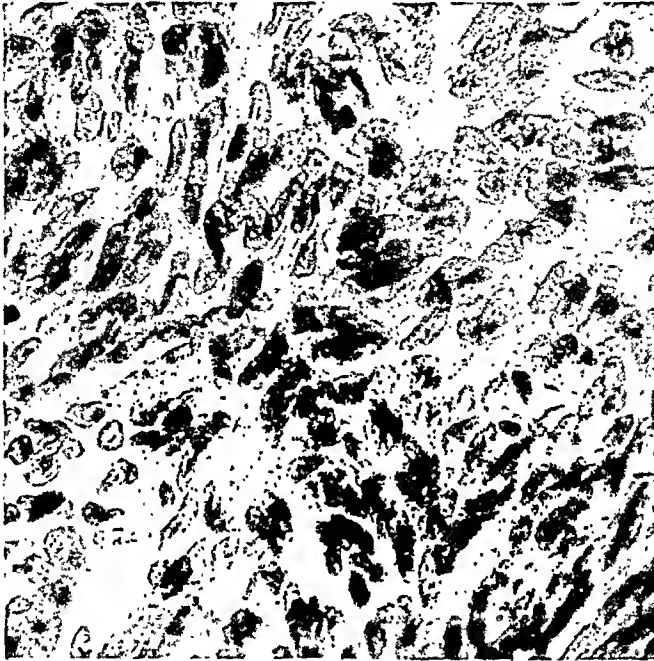


Fig. 9.—A more advanced stage of hyperplasia. Compare with Fig. 7. Hematoxylin and eosin, $\times 540$.

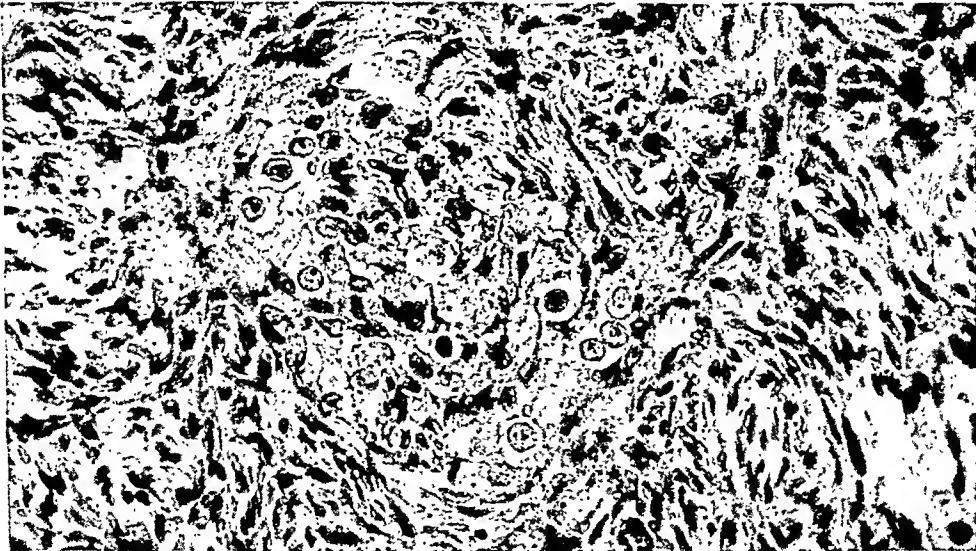


Fig. 10.—Luteinization in stromal hyperplasia. Hematoxylin and eosin, $\times 540$.

As can be seen from Table I, the age range of both carcinoma and control cases was from 30 years to over 70 years. The oldest patient in the carcinoma group was 74 years of age. There was one case of a 26-year-old woman with endometrial malignancy. It was included in the fourth decade group.

A problem arose in the cases where radiation therapy was given before hysterectomy. Only in a few such was there a characteristic effect on the ovarian vessels and stroma. In most, the ovary appeared to be well preserved and showed the various changes with the same frequency as the nonradiated cases. It was decided, therefore, to include the total group of 34 in the general category and apply the same criteria of stromal hyperplasia.

From Table I it is also seen that stromal hyperplasia is present in 36 to 43 per cent of the controls. It reaches its height in the fifth decade, and then tends to subside both in incidence and degree of activity with advancing age. In the carcinoma series there is a significantly higher and increasing incidence in all decades past 30 years (56 to 92 per cent). It persists well into advanced senility, and retains morphological evidence of vigor. Our study of the premenopausal ovary, based on the daily experience with a large amount of material in a laboratory of gynecologic pathology, and a small sampling study, leads us to conclude that stromal hyperplasia is extremely rare in the woman before the fourth decade and uncommon before the fifth decade.

Cysts—Simple, Follicular, Theca, and Corpus Luteum.—From Table II it is seen that there is a significantly higher incidence of such cysts in the fifth and sixth decades in the carcinoma series. For the total it is over twice as common as in the control group. An impressively large number of these cysts in the tumor group are of the subinvolted theca or corpus luteum types. A question poses itself. Are such cysts a reflection, in the premenopause, of the same stimulus which produces stromal hyperplasia in senility, and is the difference accountable to the presence of primordial ova in the younger group? Herrell¹⁸ is much impressed by the cysts in the ovaries of his carcinoma group. In our study these subinvolted cysts were considered as corroborative evidence of stromal hyperplasia, although the other criteria were required for a positive diagnosis.

TABLE II. DISTRIBUTION OF OVARIAN STROMAL CELL AND GERMINAL EPITHELIUM DERIVATIVES IN CASES OF ENDOMETRIAL CARCINOMA AND CONTROLS

| AGE (YEARS) | CYSTS SIMPLE, FOLLICULAR, THECA LUTEIN CORPUS LUTEUM | | CYSTS GERMINAL INCLUSION | | CYSTOMAS | | CORTICAL GRANULOMA | | THECOMA- TOSIS | | THECOMA | |
|----------------|--|----------------|--------------------------------|----------------|--------------|----------------|-----------------------|----------------|-------------------|----------------|--------------|----------------|
| | CON- TROL | CARCI- NOMA | CON- TROL | CARCI- NOMA | CON- TROL | CARCI- NOMA | CON- TROL | CARCI- NOMA | CON- TROL | CARCI- NOMA | CON- TROL | CARCI- NOMA |
| 30 to 39 | 2 | 3 | — | 1 | — | — | — | — | — | — | — | — |
| 40 to 49 | 11 | 20 | 8 | 17 | 1 | 3 | 1 | 4 | — | — | — | 2 |
| 50 to 59 | 3 | 14 | 17 | 38 | 6 | 6 | 2 | 10 | 2 | 7 | 1 | 6 |
| 60 to 69 | — | 1 | 22 | 28 | 10 | 11 | 1 | 11 | 1 | 5 | 1 | 8 |
| 70+ | — | — | 7 | 3 | — | — | — | 1 | — | — | — | 2 |
| Total | 16 | 38 | 54 | 87 | 17 | 20 | 4 | 26 | 3 | 12 | 2 | 18 |

Germinal Epithelium Inclusion Cysts.—These structures are seen most frequently in the sixth and seventh decades both in the control and carcinoma series. They are more common in the latter group. Their relation to invagination of the germinal epithelium is usually not difficult to demonstrate. On the other hand the degree of stromal activity does not necessarily correspond to the degree of surface convolution. Although we feel that the cysts are related to stromal activity there are probably other factors, as well, which have to do with the formation of surface gyri.

TABLE I. STROMAL HYPERPLASIA OF THE OVARIES IN CASES OF CARCINOMA OF THE ENDOMETRIUM AND IN CONTROLS

| AGE (YEARS) | CASES—TOTAL | | STROMAL HYPERPLASIA | | | |
|----------------|-------------|-----------|---------------------|----------|-----------|----------|
| | CONTROL | CARCINOMA | CONTROL | PER CENT | CARCINOMA | PER CENT |
| 30 to 39 | 11 | 9* | 4 | 36 | 5 | 56 |
| 40 to 49 | 60 | 57 | 25 | 42 | 45 | 80 |
| 50 to 59 | 105 | 140 | 45 | 43 | 116 | 83 |
| 60 to 69 | 109 | 113 | 54 | 40 | 100 | 88 |
| 70+ | 22 | 12 | 8 | 36 | 11 | 92 |
| Total | 307 | 331 | 136 | 44 | 277 | 84 |

*Includes one case of a 26-year-old woman.

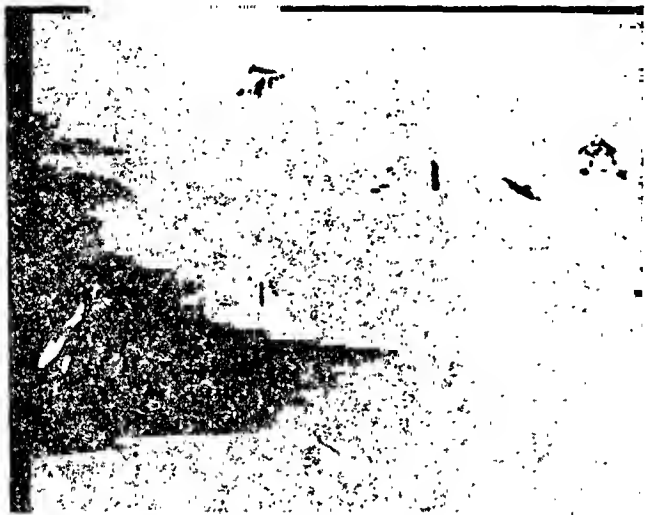


Fig. 13.—Identical area as in Fig. 12. Photographed with polarized light to illustrate the crystals.

STROMAL HYPERPLASIA OF THE OVARIES IN CASES OF
CARCINOMA OF THE ENDOMETRIUM AND IN CONTROLS

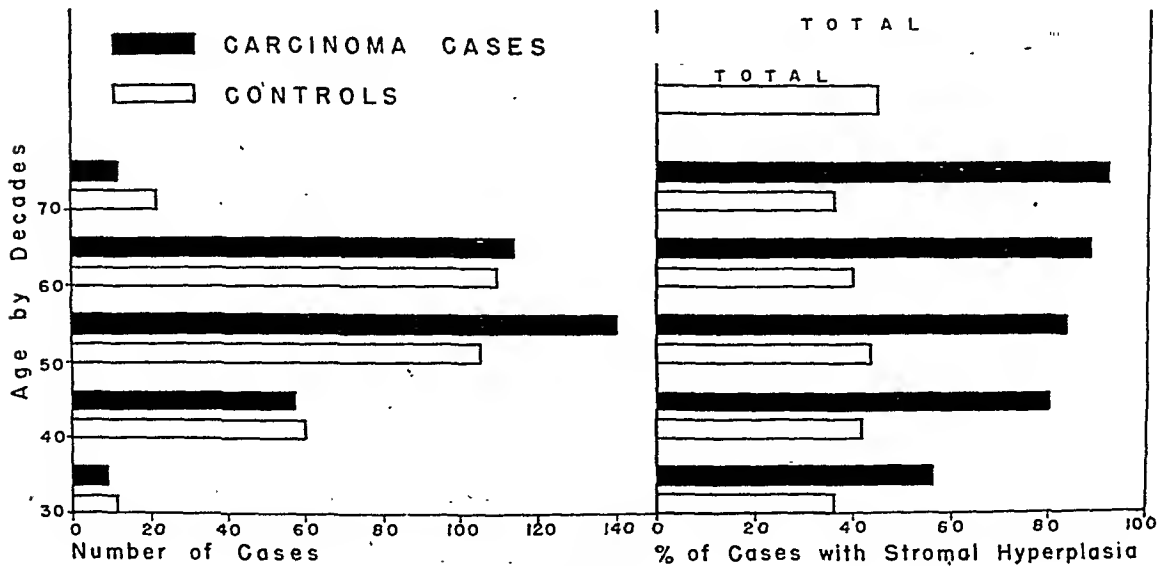


Fig. 14.

effort to respond to hypophyseal stimulation as ova and follicles are depleted. Normally, when the ovaries become senile, the endogenous production of estrogen is so low that no evidence of LH stimulation is detectable, viz., there is insignificant, if any, ovarian stromal activity and, by present methods, essentially pure FSH is the only gonadotropin secreted by the pituitary gland.

From the above considerations it seems reasonable to postulate that LH may be involved when the ovarian stroma behaves abnormally. Conceivably LH, either spontaneously secreted or stimulated by extraovarian factors (e.g., estrogen from the adrenal cortex), might in itself initiate abnormal stromal activity, even the stromal tumors. Regardless of etiology, estrogen-producing ovarian tumors probably call forth LH which in turn may play a part in their continued growth and secretory activity. The known estrogen-producing tumors are, of course, the granulosa cell tumors and thecomas. Taylor and Millan²¹ reviewed the literature concerning the association, after the menopause, of tumors other than the granulosa and thecal cell types with endometrial proliferation, and added two instances of their own, both being of the pseudomucinous variety. Smith,²² on the basis of postmenopausal endometrial proliferation, considers the cystadenofibromas, both serous and pseudomucinous, estrogenic. On the other hand, evidence that postmenopausal ovarian stromal hyperplasia is accompanied by the secretion of estrogen is not yet established,¹ though in its most pronounced development which we have termed thecomatosis, its appearance almost compels the diagnosis of thecoma.

That LH may be stimulated by extraovarian factors is becoming more than a concept. Smith and Smith^{23, 24} have collected evidence, and contributed their own, that products of protein catabolism result in pituitary LH activity. They worked with catabolized endometrium as found in fresh menstrual discharge. Pituitary gonadotropic function caused by tissue damage brings to mind the experiments of Brambell, Parkes, and Fielding,²⁵ in which the ovaries of mice exposed to x-rays were discovered to have stromal hyperplasia and to be secreting estrogen, and also the later investigations of Furth and Bitterworth,²⁶ in which x-radiation actually produced granulosa cell tumors in the ovaries of mice. Since in these studies the whole animal was exposed to x-rays, a chief factor in the accomplishment of the observed results might well have been protein catabolism from tissue damage by the radiation. In human beings the occurrence of granulosa cell tumor has been noted following irradiation.^{29, 30} Mild tissue damage might also account for the improved pituitary-ovarian function and the clinical improvement so often brought about by low dosage irradiation of pituitary and ovaries in patients with functional disturbances. In the light of this discussion, the existence of a hormonal factor in endometrial carcinoma will now be considered.

A. Estrogen as an etiological agent.—Estrogen is known to be carcinogenic in susceptible animals—in prolonged unphysiologic dosage. Conceivably, therefore, in the susceptible patient, it may tip the balance of unknowns in favor of endometrial malignancy. Crossen³¹ presents figures showing that a delayed menopause, with its prolonged estrogenic activity, is four times more frequent

Cystomas.—In this group are included the pseudomucinous, serous, and cystadenofibromatous types. The most common in both series are the pseudomucinous variants. The cystomas are present in essentially the same frequency and age distribution in the controls as in the tumor series.

Cortical Granulomas.—There is a decidedly greater incidence of these in the tumor group. The order of magnitude of their occurrence (7:1), is nearly the same as that of thecomatosis and thecoma. This supports the view that cortical granulomas represent one form of end-result of stromal hyperplasia. It is true that in a few cases the evidence of former hyperplasia is rather poor. It also must be pointed out that recognition of cortical granulomas in Zenker-acetic acid-fixed material requires closer examination and longer search than in Bouin-fixed tissue; therefore the figures on these structures in the control series are not entirely reliable.

Thecomatosis.—There is a decidedly higher incidence (4:1) of this stromal change in the carcinoma group. In several instances the diagnosis of thecoma was hard to avoid. Diffuseness of the process, absence of a capsule, failure of displacement of normal ovarian architecture, all favored the nonneoplastic character of thecomatosis.

Thecoma.—Included in this group was one case of granulosa cell carcinoma with coexistent endometrial carcinoma. All the others had the characteristics of theca cell tumors. Not included were three cases of nonestrogenic fibroma in each of the carcinoma and control series. In these no evidence of probable theca cell origin could be found. As can be seen from Table II, the incidence of thecoma in the carcinoma series is nine times as great as in the controls. It was noted that the opposite ovary, not involved by the theca cell tumor, invariably showed stromal hyperplasia, but not necessarily of a high degree of activity.

Our findings in this respect are in general accord with previous reports (Smith,²³ Novak,¹⁵ Doekerty¹⁶). In our series the incidence was 5.4 per cent of the carcinoma group, and nine times as frequent as in the controls.

Discussion

During childhood, i.e., between the ages of 5 and 8 years, estrogenic substance is found in small amounts in the urine. Its source is unknown but attributed in good part to the adrenal glands. According to direct evidence in animals and circumstantial evidence in human beings, estrogen stimulates the secretion of luteinizing hormone (LH) by the anterior lobe of the hypophysis and causes its release. Experimentally LH, in combination with amounts of anterior hypophyseal follicle stimulating hormone (FSH), too tiny in themselves to bring on the follicular secretion of estrogen, causes the nonfibroblastic cells of the ovarian stroma to secrete estrogen. The morphologic stromal cell activity at puberty, noted by Wallart,¹⁴ would seem then to be the result of gradually intensified LH ovarian stroma interaction, first preliminary to and then concomitant with cyclic follicular activity. It seems likely that the ovarian stroma contributes to the estrogen secreted by the ovaries until they are exhausted of their follicles, and thereafter is the only source of whatever estrogen they may secrete. The incidence of stromal hyperplasia between the ages of 30 and 40 years and its peak between 50 and 60 years probably is in inverse proportion to the number of extant ova and follicles, and very likely represents a compensatory

material. Sections of the ovary from early infancy to old age obtained at autopsy were also studied with the aid of connective tissue, reticulum and nuclear stains, to determine the changes in the stroma throughout life.

Conclusions

1. The ovarian stroma has the competence to differentiate into the cells of the granulosa, theca interna, corpus luteum, and corpus albicans.

2. This process normally follows an orderly sequence, possibly regulated by the ovum.

3. In senility this differentiation recapitulates the normal sequences, but in disorderly manner, leading to stromal hyperplasia, thecomatosis, cortical granuloma formation, and granulosa and theca cell tumors.

4. Stromal hyperplasia makes its appearance in the early period of senescence (fourth and fifth decades), reaches its height in the sixth decade, and thereafter tends to subside with old age.

5. Stromal hyperplasia is significantly more frequent in cases of endometrial carcinoma (56 to 92 per cent) than in a control group (36 to 43 per cent) and persists into advanced old age.

6. The thecoma, a stromal derivative, is significantly more common in carcinoma of the endometrium than in the control series (9:1).

7. Subinvolved corpora lutea and theca lutein cysts are seen in the fifth and sixth decades of life, and are more common in cases of endometrial carcinoma than in the control series in the same decades.

8. The existence of hormonal factors in endometrial carcinoma is discussed.

The authors gratefully acknowledge the aid of Dr. T. D. Kinney of the Peter Bent Brigham Hospital and Dr. S. Farber of the Children's Hospital for making the material in their laboratories available for this study.

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in those developing endometrial cancer than in controls. That the role of estrogen per se may be a minor one, however, is indicated by (1) the fact that a larger number of women do not get cancer of the endometrium, (2) that this cancer occurs many years after the menopause in patients in whom there has been no known intervening exposure to estrogen, and (3) that it may occur long after castration. Smith¹ reported three instances, 15, 17, and 30 years, respectively, following bilateral oophorectomy.

B. The concomitant condition of the endometrium and ovaries in carcinoma of the endometrium.—A significant, though far from constant association of endometrial proliferation with carcinoma has been found.^{1, 17, 18, 19} In the present state of knowledge endometrial proliferation must necessarily be interpreted as reflecting secretion of estrogen by the ovaries. Although some estrogen is excreted after ablation of the ovaries and assumed to be of adrenal origin, it has not been reported as sufficient to cause endometrial proliferation. Herrell¹⁸ was impressed by the cysts in the ovaries of his carcinoma group and, as already stated, the incidence of cysts in patients of our own group between the ages of 40 and 60 years is over twice as great as in the controls, an impressively large number being of the thecal and corpus luteum types. These are the result of FSH-LH stimulation. These, with the cystomata, thecomas, thecomatoses and stromal hyperplasias, add up to well over an 80 per cent incidence of ovarian activity in our series of cases with endometrial carcinoma. How explain the striking association of ovarian activity with endometrial cancer? If the ovarian activity is an etiological factor in endometrial carcinogenesis what causes such activity? A possible answer to the first question is presented in the following paragraph.

Cancer of the endometrium is characterized by bleeding and discharge, both of which are signs of tissue breakdown, protein catabolism. On the basis of the first part of this discussion, the absorption of products of protein catabolism would be expected to stimulate the secretion and release of anterior pituitary LH which, in combination with FSH, would strongly stimulate in the ovaries any cells still capable of responding, thus perhaps accounting for the ovarian and endometrial findings in patients with the disease. In those patients with inactive ovaries and endometrium in the presence of endometrial cancer there could be postulated (1) insufficient absorption of protein breakdown products to give adequate anterior lobe stimulation, or (2) complete absence of cells in the ovaries capable of responding to gonadotropic stimulation. The state of the ovaries in patients with endometrial cancer then might depend on the amount, rate, and duration of absorption of the products of protein catabolism in the uterus, presumably originating for the most part from cancer tissue. As a corollary of this theory, it would be necessary to find some other focus of protein catabolism in those postmenopausal women with active ovaries and without endometrial cancer to account for the initiation of the chain of events resulting in ovarian stimulation and endometrial proliferation, e.g., in ovarian tumors themselves, in tumors elsewhere in the body, in local or systemic areas of infection, from cardiovascular disease, etc. Protein catabolism and pituitary stimulation may have far-reaching ramifications, and conceivably could play a part in hyperplastic changes in the female breast, in prostatic hypertrophy, in various other endocrine and metabolic dysfunctions, even in the etiology of tumors.

Summary

Routine sections of the ovary from 331 cases of carcinoma of the endometrium were studied, and the findings compared with a control group of approximately the same number and age distribution obtained from selected autopsy

A CORRELATIVE STUDY OF ADENOMYOSIS AND PELVIC ENDOMETRIOSIS, WITH SPECIAL REFERENCE TO THE HORMONAL REACTION OF ECTOPIC ENDOMETRIUM

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THE term adenomyosis, as it is generally employed, refers to the noneoplastic condition in which the uterine mucosa exhibits a benign invasion into the uterine musculature. There is no submucosa in the uterus, so that the endometrium is in direct contact with the muscularis, its under surface being closely applied to the latter, and dipping for short distances into the interstices of the musculature. The benign invasion seen in adenomyosis may extend for only a comparatively short distance, or it may penetrate even to the serosa, thus giving rise to a variety of secondary pelvic endometriosis, though not, of course, the common one.

Even in a normal uterus the mucosal indentations into the musculature may at times be fairly deep, so that it is difficult to draw any sharp line between such normal irregularities and actual adenomyosis. In the latter, however, the mucosal invasion is much more pronounced, and is always combined with overgrowth of the muscularis, with grossly a greater or lesser degree of thickening of the uterine wall in the involved areas. The fact that estrogen is the normal growth hormone of both the mucosa and the muscularis has naturally led to the suspicion that adenomyosis is a hormone-induced lesion, but there is certainly no direct evidence on this point.

The abnormal endometrial growth propensity which forms a part of adenomyosis is quite different from that seen with endometrial hyperplasia, the lesion which above all others is believed to be due to an excessive and abnormally persistent estrogen growth effect. While the surface mucosa in cases of adenomyosis may show a typical Swiss cheese hyperplasia, in other cases it may be entirely normal, with a normal response to progesterone as well as to estrogen. The conspicuous growth abnormality of the surface endometrium in the case of adenomyosis is manifested by the downward penetration into the muscularis of a mucosa which normally, whatever its hormonal response may be, respects the normal barrier between the mucosa and the muscularis.

In spite of this distinction, one cannot resist the feeling that there is some common denominator between endometrial hyperplasia and adenomyosis, and possibly also pelvic endometriosis. As a matter of fact, the designation internal or uterine endometriosis is used by many authors for adenomyosis. The wisdom of this seems to us rather doubtful, not only because of the confusion it creates with the common variety of external endometriosis, but even more because the

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Adenomyosis With Endometrial Hyperplasia

In 36 of the cases (36.3 per cent) the surface mucosa showed a hyperplasia pattern, while in the remaining 63 (64.9 per cent) it showed one phase or another of a normal estrogen-progesterone cycle, with the exception of two cases in which the endometrium was of senile atrophic type. Since the age of the 36 patients in this group averaged 50.2 years, it is not surprising that the hyperplasia pattern of the endometrium was often of the retrogressed variety seen so often beyond the menopause.

TABLE I

| | AGE | 21-30 | 31-40 | 41-50 | 51-60 | 61 AND BEYOND |
|---|--------|-------|-------|-------|-------|------------------|
| Adenomyosis without hyperplasia (63 cases) | Number | 3 | 23 | 31 | 5 | 1 |
| Adenomyosis with hyperplasia (36 cases) | Number | - | 5 | 15 | 12 | 4 |
| Adenomyosis with endometriosis and without hyperplasia (31 cases) | Number | 1 | 11 | 15 | 3 | 1 |
| Adenomyosis with endometriosis plus hyperplasia (11 cases) | Number | 1 | 2 | 5 | 2 | 1 |
| Endometriosis without hyperplasia (92 cases) | Number | 31 | 39 | 20 | 2 | - |
| Endometriosis with hyperplasia (10 cases) | Number | - | 3 | 6 | 1 | - |

In no case of this subgroup of 36 cases showing surface hyperplasia was the ectopic endometrium of functioning type. Always it showed a proliferative picture, with a Swiss-cheese hyperplasia in at least 18 cases. In at least one case a large cystic gland was found to be full of blood, indicating that bleeding may occur in islands of purely proliferative ectopic endometrium, just as it may occur from the purely proliferative surface endometrium in cases of anovulatory menstruation.

In the study of our material we were interested to note that the most active and extensive cases of adenomyosis were those in which there was marked hyperplasia of the basal layer of the surface mucosa, whether the latter was of functional or purely proliferative type. It is not uncommon to see a thickened, proliferative basalis, even of Swiss-cheese type, in an otherwise typical progestational endometrium. The basalis represents the growing portion of the mucosa, and is under the hormonal growth influence of estrogen alone, the immaturity of its cells making them unresponsive to the differentiating hormone, progesterone. It is therefore not surprising that when there is a hyperplastic overgrowth of the basalis, the latter may give further evidence of its proliferative tendency by pushing down into the muscularis, with the production of adenomyosis.

The ovaries were available for study in 20 of the 36 cases in this hyperplasia group. All of them showed follicle cysts with or without well preserved granulosa cells, which might be expected. However, in three cases corpus luteum structures were noted, including two of corpus luteum hematoma and one of corpus luteum cyst. An occasional corpus luteum in cases of hyperplasia has been noted by others (Novak and Martzloff). The finding of corpus luteum structures, active or retrogressive, in such cases is probably to be interpreted as representing beginning ovulatory activity in previously anovulatory women or relics of previous ovulations in women who more recently have been anovulatory.

histogenesis of the internal and external varieties of endometriosis is entirely different, whatever the origin of the external form may actually be. On this latter point there is still much uncertainty, but this question calls for no review in this paper.

The fact that there are certain points in which either the histogenesis or the hormonal responsiveness of these three lesions appear to make contact, and that either two or all three of these not infrequently coexist, made it seem worth while to review our material from this standpoint, and this correlative study constitutes one of the purposes of this paper.

The other has to deal with the fact that in both adenomyosis and pelvic endometriosis we are dealing with ectopic endometrium, and the question arises as to whether this endometrium exhibits hormonal reactions similar to that of the uterine mucosa proper, with which it may be histologically identical. The general statement is often made that it does react to the ovarian hormones just as does the surface mucosa, but our studies indicate that this is not by any means always the case. The investigation of this point constitutes the second purpose of this paper.

Material

The material on which this study is based comprises 243 patients with cases of adenomyosis and pelvic endometriosis which were operated upon in the private service of the senior author in Bon Secours Hospital in the eight-year period extending from 1938 to 1946. Adenomyosis alone was found in 92 cases, pelvic endometriosis alone in 102, while in 42 cases both these lesions were present. In a considerable proportion of all groups, other conditions, such as myomas, were likewise present, but would seem to have no bearing on the present discussion. We may add, also, that the occasional cases of adenomyosis with penetration to the uterine serosa were not included in the series of cases of pelvic endometriosis. In many of the adenomyosis cases one or both ovaries were available for study, and in many of the pelvic endometriosis group the endometrium of the uterus was likewise available, so that correlative studies were all the more readily possible. While, as we shall see, ovarian endometriosis is not uncommon in cases of adenomyosis, our experience convinces us that the frequency of this coexistence would be much greater than we found it if it were possible to study both ovaries thoroughly in all cases. Very frequently, and very properly, one or both ovaries are conserved, but endometriosis is not infrequently present, perhaps deep beneath the surface of such ovaries. This can be stated on the basis of the study of a number of such grossly normal ovaries, or ovaries showing grossly only follicle cysts, which were removed with the uterus in some of our cases of adenomyosis. Not always is ovarian endometriosis a hemorrhagic lesion, and the nonhemorrhagic, usually microscopic lesions, are likely to be overlooked. In any event the fact that in the 243 cases of this series, both adenomyosis and pelvic (usually ovarian) endometriosis were coexistent in no less than 42, is at least suggestive of some sort of relationship between the two.

The general grouping of the 243 cases, together with the age incidence in the various groups, is summarized in Table I.

In the 99 cases showing only adenomyosis, the lesion was of various degrees, the ectopic endometrium being limited to the inner third of the myometrium in 65, involving two-thirds of the muscularis in 23, and the whole thickness in 11 cases.

endometrium in every case was of nonsecretory type, five showing Swiss-cheese hyperplasia, and two an early interval picture. This again emphasizes the immature nature of the invading endometrium.

(d) Decidual changes in the surface mucosa were seen in two cases in which there had been a recent pregnancy, although no villi were seen. In one case, however, one of the ovaries was available for study, and it showed a typical corpus luteum of pregnancy. No evidence of decidual change was seen in the ectopic endometrium of either of these cases, again illustrating the usual refractoriness of the ectopic endometrium to the full hormonal response of which the functional layers of normal endometrium are normally capable. There are, of course, exceptions to this rule, since the aberrant mucosa is certainly in a minority of cases of functioning type, which can under the influence of both estrogen and progesterone exhibit either progestational or even decidual changes, as we have observed in an occasional case.

(d) Senile surface endometrium was seen in two cases, with similar changes in the aberrant mucosa.

Adenomyosis Combined With Pelvic Endometriosis

In 42 patients there was a co-existence of adenomyosis and pelvic endometriosis. The adenomyosis in 31 of the cases was limited to the inner third of the muscularis, the inner two-thirds in six, and it involved the whole thickness of the uterine wall in three. The pelvic endometriosis, with some overlapping of groups, involved the ovaries in thirty-two cases (five bilateral), the tubes in nine (three bilateral), the pelvic serosa in two, and the appendix in one (no other pelvic endometriosis).

In eleven cases the surface mucosa of the uterus showed a typical Swiss-cheese hyperplasia, while in the remaining thirty-one it was presumably of fully cyclical type (seventeen secretory, nine interval nonsecretory, three postmenstrual, one menstrual, and one senile).

(a) In the eleven patients with surface hyperplasia, the ectopic mucosa was in every case of proliferative variety, showing Swiss-cheese hyperplasia in six, interval nonsecretory in three, and postmenstrual in two. No blood was found in the gland lumina of any of these cases.

In the eleven cases of this group the associated endometriosis involved the ovaries alone in nine, the tubes alone in one, and both ovaries and tubes in one. In contrast with the invading endometrium of adenomyosis the ectopic pelvic endometriosis characteristically shows a hemorrhagic tendency, this appearing in nine cases. In six of these, typical endometrial blood-containing ovarian cysts were noted. In none of them, however, was there any evidence of secretory response, just as was found with the aberrant endometrium of adenomyosis, suggesting that in both conditions the ectopic endometrium is of immature, not fully functioning type.

(b) In 31 cases of combined adenomyosis and pelvic endometriosis in which the uterine surface mucosa was presumably of functional type, the ectopic endometrium of the adenomyosis was of nonsecretory type in every case. The aberrant mucosa of the pelvic endometrium was not so easily analyzed, as in a considerable group endometrial cysts were present in which much of the mucosa was lost. In one such case secretory glands were seen adjoining such a cyst, and it is quite possible that in others the mucosa might also have been of functioning type, though this could not be demonstrated histologically. The presence of the blood cannot be considered as definite evidence of an estrogen-progesterone type of menstrual bleeding, as bleeding can also occur from endometria as a result of estrogen stimulation alone. The fact that hemorrhage is so much more common in the aberrant endometrium of pelvic endometriosis than that of adeno-

Adenomyosis Without Hyperplasia of the Endometrium

In this group there were 63 cases, varying in age from 24 to 64 years, and they may be subdivided into the following groups.

(a) Progestational endometrium was noted in 14 cases, and the most striking feature of this group was that, without a single exception, the invading islands of endometrium in the uterine wall were of nonsecretory type, and in none of these was there any evidence of blood. All the ectopic endometrium, therefore, was of the unripe, immature variety responsive only to estrogen, but not to progesterone. In six of the cases the ectopic endometrium showed a Swiss-cheese hyperplasia, in seven it was of early interval type, and in one it resembled the postmenstrual phase. It is of further interest that in four of the six cases in which the ectopic mucosa showed hyperplasia, there was similar marked hyper-



Fig. 1.—High power of blood-containing gland in ectopic endometrium of a case of adenomyosis, the surface mucosa showing hyperplasia.

plasia of the basalis of the otherwise progestational surface mucosa. The significance of this fact, as indicating the probable origin of adenomyosis from the basalis, has already been commented upon.

(b) Proliferative, nonsecretory surface endometrium was noted in 17 cases, 13 corresponding to an early interval phase, and 4 postmenstrual. In every one of these the ectopic mucosa was likewise of proliferative type. In only 1 case was there evidence of bleeding in the invading endometrial islands, a large dilated gland showing a considerable amount of blood within its lumen. The ovaries of this case were not available for study, but it seems reasonable, in view of the proliferative picture of both the surface and the invading mucosa, that the cycles were probably of anovulatory type. There is no reason why bleeding might not occur in the ectopic mucosa of anovulatory patients, just as it occurs from the surface mucosa, usually with only slight evidence of histologic regression.

(c) Menstruating endometrium was found on the surface of seven uteri which were removed during a menstrual period, in six of ovulatory, and one of anovulatory variety, on the basis of correlated ovarian study. The aberrant

Pelvic Endometriosis Alone

In this series there were 102 cases of pelvic endometriosis, without associated adenomyosis. In 53 of these the uterus was available for study, having been removed either because of extensive endometriosis in women of the older age



Fig. 4.—Showing how the basalis invades the muscularis in a case of adenomyosis.



Fig. 5.—Marked Swiss-cheese hyperplasia pattern of basalis in a case of adenomyosis.

group, or for other indications, usually uterine myoma. In eleven others curettage had been done, so that the endometrium was available for study. The following sites of endometriosis were noted: ovaries, eighty-four; tubes, fifteen; uterine serosa, five; appendix, six; sigmoid, one; rectum, three; vesicouterine peritoneum, two; and broad ligament, one.

myosis might suggest that a full menstrual response is more common with the former, but histologic proof of this is difficult. Again, no conclusions can be drawn from the twelve cases in which the ectopic pelvic endometrium was of interval nonsecretory or postmenstrual type, as endometrium of these types might occur whether the cycles are ovulatory or nonovulatory. In the one case



Fig. 2.—Showing invading basalis in case of adenomyosis, the surface mucosa being typically progestational. Pelvic endometriosis was also present in this case, the aberrant endometrium being of immature, nonsecretory type.



Fig. 3.—An area of immature, nonsecretory type deep in the muscularis of case shown in Fig. 2.

of this group in which operation was done on the first day of menstruation, the presence of a few desquamating secretory cells on the surface of the endometrial cyst make it seem certain that the endometrium was of fully functioning type.

The common finding of blood in pelvic endometrial lesions cannot be linked up with a recent menstrual period, as the blood persists and is to be found at any phase of the cycle. In three of the cases in this group the operation had been done during a menstrual bleeding, and in two of these, on the basis of the absence of any corpus luteum in the ovaries, the cycles were thought to be anovulatory. In both of these the ovarian endometrium was of Swiss-cheese type.



Fig. 8.—Progestational endometrium in uterus with nonsecretory endometrium in ovary (see Fig. 9).

Finally, there remains the group of 38 cases of endometriosis in which neither the uterine nor even the excised mucosa were available for study, and in which no correlation was possible except on the basis of menstrual chronology. Because of the very limited value of this group in our present study we shall not detail the findings. Suffice it to say that almost without exception the pelvic endometrial islands were of proliferative, nonfunctioning type.

Incidence of Endometrial Hyperplasia With Adenomyosis and Pelvic Endometriosis

The frequent co-existence of endometrial hyperplasia with both adenomyosis and endometriosis has been noted by various authors (Novak and Martzloff, Jeffcoate and Potter, Witherspoon, Smith, Haydon, and others). In our series the incidence of this combination was 23.4 per cent for the entire group, comprising 36.3 per cent in the cases of adenomyosis alone, 9.8 per cent in those of pelvic endometriosis, and 26.1 per cent in those with both adenomyosis and endometriosis.

The fact that adenomyosis and pelvic endometriosis so frequently coexist is at least suggestive of some common denominator in their causation, most likely hormonal. However, since we know so little of the etiology of either condition, especially adenomyosis, we can for the present only speculate as to the nature of their relation. Hyperplasia of the endometrium may perhaps be drawn into this group of possibly interrelated lesions, since it is frequently found combined with the other two. The fact that there are numerous exceptions to this last named combination does not negate the possibility of some sort of common denominator between them.

A correlative histologic study of the surface mucosa of the uterus and the ectopic pelvic peritoneum was therefore possible in 64 cases, while in the remaining 38 the only correlation possible was between the chronological menstrual phase and the histology.



Fig. 6.—Typical progesterational endometrium of uterus in which the aberrant ovarian endometrium is of proliferative, nonsecretory variety (see Fig. 7).

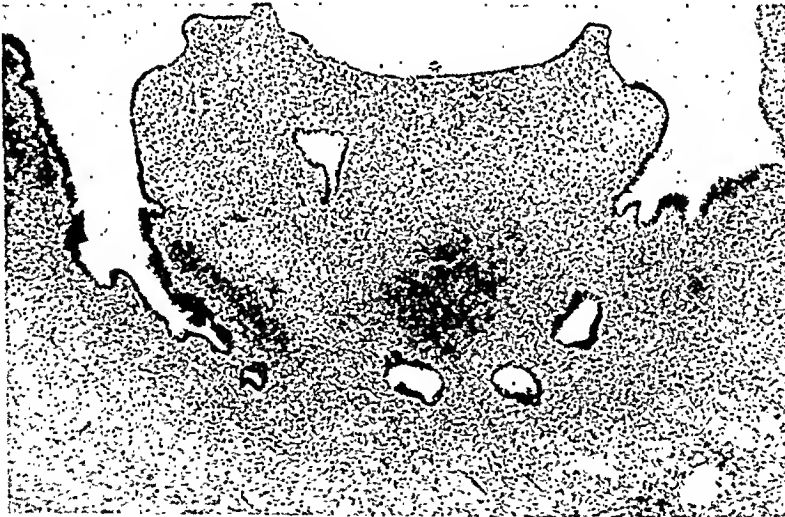


Fig. 7.—Immature nonsecretory endometrium in ovary of case showing marked progesterational endometrium in uterus. (Fig. 6.)

In ten cases in which the uterine mucosa showed a Swiss-cheese hyperplasia the aberrant pelvic endometrium showed also a proliferative endometrium. In the remaining 54, the uterine endometrium was of secretory, early interval or postmenstrual variety and presumably of fully functioning type. Only six showed definite secretory changes in the pelvic endometrium, but it is quite sure that a number of others, especially those with definite chocolate cysts, were likewise of this type, though we could not demonstrate this histologically.

The incorrectness of this statement, aside from the objective evidence we have presented, is explained by the fact that the aberrant endometrium of both adenomyosis and endometriosis is usually of an immature variety, its immaturity being evidenced by the fact that it is physiologically responsive only to the growth stimulus of estrogen, and not to the differentiating influence of progesterone. There are, of course, some exceptions, the exact incidence of which it is difficult to set down with any accuracy, because of the frequent difficulty, especially in ovarian endometriosis, of gauging the functional status of the lining of hemorrhagic cysts from which most of the lining has been lost.

It so happened that in the present series the ectopic endometrium of adenomyosis showed no histologic evidence of secretory activity in any case, regardless of whether or not the surface mucosa was of secretory type. This was rather surprising to us, since we have noted secretory changes in the ectopic mucosa of at least an occasional case of adenomyosis, though none was encountered in this particular series. Certainly, however, there can be no doubt that in the vast majority of cases the ectopic endometrium is of immature type, responding to the growth effect of estrogen but not to the differentiating effect of progesterone.

Another interesting feature of the general problem has been the common occurrence of bleeding in ovarian and other forms of pelvic endometriosis, and to a far smaller extent in the aberrant mucosa of adenomyosis, even when such ectopic endometrium is clearly of purely proliferative type. This, after all, is not surprising, since anovulatory menstruation and anovulatory functional bleeding have their source from a purely proliferative uterine surface mucosa. Just why this hemorrhagic tendency is so much more marked in the case of endometriosis than in that of adenomyosis is not clear, although one factor which suggests itself is the immediate proximity of the ovarian endometrium to the source of production of the ovarian hormones.

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Coexistence of Myoma With Adenomyosis and Pelvic Endometriosis

The incidence of myoma in our series of 243 cases of adenomyosis and endometriosis was 37.5 per cent for the former and 29.8 per cent for the latter, or 33.7 per cent for the combined group. This is somewhat lower than the figures for similar groups reported by others (Fallas and Rosenblum, 41.5 per cent; Smith, 41.6 per cent). The association of myoma with these lesions is probably coincidental, as myoma is a definite neoplasm of unknown etiology, and there is little support for the hypothesis that it may be of endocrine causation. On the other hand, neither adenomyosis nor endometriosis are neoplastic, and there is more justification for suspecting the possibility of an endocrine factor in their production.



Fig. 9.—Nonsecretory endometrium in ovary, associated with progesterational endometrium in uterus (Fig. 8).

Comment and Summary

The existence of a definite hyperplasia of the endometrium is commonly taken to be evidence of an anovulatory cycle, but this interpretation is acceptable only when applied to the uterine surface mucosa. It would not be justified from examination of the ectopic endometrium of adenomyosis and endometriosis, since this is often of hyperplastic type even when the surface mucosa is secretory. We therefore disagree with the suggestion of von Numerus that anovulatory cycles, assumed only on the basis of examination of the ectopic endometrium, may actually be of importance in the production of adenomyosis and pelvic endometriosis, or that they necessarily explain the common sterility seen with the latter. It is obvious, also, from the results of our own studies, that we cannot agree with the statement of Jeffcoate and Potter that "since the ectopic endometrium reacts to ovarian hormones in exactly the same way as does the uterine mucosa, its histologic appearance permits an estimation of ovarian function, normal or otherwise."

TABLE I. ANALYSIS OF DATA
CASES OF PROVED SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN

| CASE | PA- TIENT | AGE | PAR- ITY | GRA- VID- ITY | PELVIS | CARDIAC DIAGNOSIS | COMMENT |
|------|--------------|-----|-------------|---------------------|--------|---|--|
| 1. | G. O. | 34 | 2 | 3 | Normal | Rheumatic Enlarged heart MI MS N. S. R. Class 1B | S. B. E. 8 months prior to pregnancy Vaginal delivery. Mother, baby well |
| 2. | I. J. | 38 | 4 | 6 | Normal | Rheumatic Enlarged heart MI MS N. S. R. Class 2B | S. B. E. 12 months prior to pregnancy Vaginal delivery. Mother, baby well |
| 3. | C. L. | 17 | 0 | 1 | Normal | Rheumatic Enlarged heart MI MS AI N. S. R. Class 1B | S. B. E. 17 months prior to pregnancy Vaginal delivery. Mother, baby well |
| 4. | F. J. | 27 | 0 | 2 | Normal | Rheumatic Enlarged heart MI MS N. S. R. Class 3C-4E | S. B. E. in fifth month of pregnancy Vaginal delivery. Mother, baby well |
| 5. | V. D. | 25 | 1 | 2 | Normal | Rheumatic Enlarged heart MI MS N. S. R. Class 3C-4E | S. B. E. in eighth month of pregnancy Vaginal delivery. Mother, baby well |

MI-Mitral insufficiency

MS-Mitral stenosis

AI-Aortic insufficiency

N. S. R. Normal sinus rhythm

Class-Functional and therapeutic of the New York Heart Association (see text)

S. B. E. Subacute bacterial endocarditis

CASE 1.—G. O. Subacute bacterial endocarditis in April, 1945. Blood cultures showed *streptococcus viridans* sensitive to 0.08 units of penicillin per c.c. The patient received 32 million units of penicillin over forty-two days and recovered. All subsequent blood cultures were negative. She became pregnant eight months later, at which time the heart showed slight enlargement but the electrocardiogram, vital capacity (4,000 c.c.), and exercise tolerance were normal. The functional classification was 1B. Pregnancy was allowed to continue. The patient went through an entirely uneventful pregnancy and labor without any evidence of cardiac strain. She had a fifteen-hour labor at 42 weeks' gestation and was delivered by low forceps under gas, oxygen, ether anesthesia. The baby weighed 3,600 Gm. The pulse and respirations remained normal throughout labor. The blood loss at delivery was estimated at 150 c.c. Penicillin was given for three days postpartum and mother and baby were discharged well on the tenth day. Follow-up examination one year later revealed no change in the cardiac status.

CASE 2.—I. H. Subacute bacterial endocarditis in May, 1945. Blood cultures showed *streptococcus viridans* sensitive to 0.08 units of penicillin per c.c. The patient received seven million units of penicillin over twenty-six days and recovered in spite of an embolus to the right femoral artery. All subsequent blood cultures were negative. In July, 1945, a cholecystostomy and choledochotomy were performed. The patient received penicillin for the first two days after operation and recovery was uneventful. She became pregnant in May, 1946, and was admitted to the hospital for study in the third month of pregnancy. The heart showed slight enlargement but the electrocardiogram, vital capacity (3,100 c.c.), circulation time, and exercise tolerance were normal. The functional classification was 2B. The blood

PREGNANCY AND SUBACUTE BACTERIAL ENDOCARDITIS*

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PRIOR to the introduction of antibiotics, particularly penicillin and, to a more limited extent, streptomycin, subacute bacterial endocarditis was usually a fatal disease. Pregnancy was rarely complicated by this condition and therapy in the presulfonamide and sulfonamide eras was directed toward supporting the strength of the mother in the hope of obtaining a living child.

Stander¹ was able to find only eighteen authenticated cases of subacute bacterial endocarditis in pregnancy. The development of effective antibiotics has greatly improved the outlook for the patient with this disease and has created a relatively new problem in obstetrics. Hamilton² sent questionnaires to obstetricians and cardiologists and reports were received of seventeen women treated with penicillin for subacute bacterial endocarditis during pregnancy or the puerperium. Six died during pregnancy and three others died within the next five months, giving a total mortality of 53 per cent. The fetal mortality was 24 per cent. Eleven patients cured of the disease prior to pregnancy all survived childbirth. Three of the eleven were aborted therapeutically. Dobson³ reported a case of subacute bacterial endocarditis during pregnancy in which hysterotomy was performed at eighteen weeks' gestation "because it was felt that pregnancy might have an unfavorable influence on the course of the disease." The patient recovered. Davis and Wortmann⁴ also reported a case during pregnancy, cured with penicillin and carried to viability, at which time a cesarean section and hysterectomy were performed. There had been two previous cesarean sections for cephalopelvic disproportion. The patient obtained a living child but had serious residual cardiac damage.

Present Study

There have been ten cases with a diagnosis of subacute bacterial endocarditis complicating pregnancy in some 50,000 patients at the New York Lying-In Hospital from 1932 through 1947. The incidence of this complication is 0.02 per cent. Three cases with positive blood cultures occurred before the use of penicillin and all died during pregnancy or the puerperium. Seven cases, treated with penicillin, survived pregnancy and delivered normal living children. Two of the penicillin-treated cases had clinically authentic subacute bacterial endocarditis during pregnancy, unconfirmed by positive blood cultures. Five of the penicillin-treated cases were proved by positive blood cultures: three had recently recovered from the disease prior to the pregnancy under consideration, and two developed the disease during pregnancy. The purpose of this study is to review these five proved cases treated with penicillin in an attempt to evaluate the significance of subacute bacterial endocarditis prior to and during pregnancy. Table I summarizes the experience with the five patients.

*Read before the Section of Obstetrics and Gynecology of the New York Academy of Medicine on Feb. 24, 1948.

CASE 5.—V. D. The patient was first seen in the eighth month of pregnancy, with the classical picture of subacute bacterial endocarditis and early cardiac decompensation. Blood cultures revealed *streptococcus viridans* sensitive to 0.13 units of penicillin per c.c. Penicillin was started together with digitalis and other cardiac measures. Several days after admission, the patient developed a mesenteric infarct and went into spontaneous premature labor. After two hours of labor, she had a normal delivery under open-drop ether. The baby weighed 1,860 Gm., was transferred to the premature nursery, and survived. The mother's pulse remained above 120 and the respirations above 36 throughout labor. The blood loss at delivery was measured at 100 c.c. The patient also received sulfadiazine with soda bicarbonate for the first two days postpartum. Decompensation became more marked and the patient had to be placed in an oxygen tent. The postpartum course was febrile and further complicated by multiple emboli to the spleen, extremities, and brain. Heparin was started on the third postpartum day, followed by dicumarol. The latter was stopped six days later when evidence of subarachnoid hemorrhage developed. A total of 18 million units of penicillin was given. The patient recovered after a stormy and critical course.

Discussion

Subacute Bacterial Endocarditis Prior to Pregnancy.—The cases in the literature as well as those reported in this study, indicate that a past history of subacute bacterial endocarditis is not necessarily a contraindication to subsequent pregnancy. Healing of the endocardial lesions may result in progressive scarring and calcification of the heart valve. Moore² concludes from autopsy studies that it takes from three to six months for complete healing. The intervals between subacute bacterial endocarditis and pregnancy were eight, twelve, and seventeen months in the present series. The cardiac pathology had become stabilized in all three patients. It would appear advisable to defer pregnancy until at least six months after the disease has been cured. This interval would allow for the possibility of relapse. The advisability of childbearing should then be determined by the current cardiac status, and accepted concepts of management of the underlying heart disease followed during pregnancy, delivery, and the puerperium. Most cases of subacute bacterial endocarditis occur where the valvular endocardium has been congenitally deformed or damaged by rheumatic fever. Many of the features of the management of rheumatic heart disease complicating pregnancy have been illustrated in the foregoing cases. A comprehensive outline follows:

The cardiac status is evaluated when the patient is first seen. Information is obtained regarding age, history, general physical condition, anatomic lesion, heart size as determined by anteroposterior and lateral roentgen studies, electrocardiographic findings, vital capacity, and exercise tolerance. The exercise test should not be performed indiscriminately in the patient with borderline cardiac reserve, for the test itself may cause decompensation. The patient is then classified according to the criteria of the New York Heart Association:

CLASS 1.—Patients with cardiac disease and no limitation of physical activity. Ordinary activity does not cause discomfort. Patients in this class do not have symptoms of cardiac insufficiency nor do they experience anginal pain.

CLASS 2.—Patients with cardiac disease and slight limitation of physical activity. They are comfortable at rest. If ordinary physical activity is undertaken, discomfort results in the form of undue fatigue, palpitation, dyspnea or anginal pain.

pressure was 140/90 but the eyeground and renal function tests, including blood chemistry, urea clearance, dye excretion, and dilution concentration were all normal. The pregnancy was allowed to continue and the patient was discharged, to be followed in the antepartum cardiac clinic. The course was uneventful until the fifth month, when the patient developed an attack of bronchitis. She was admitted to the hospital, digitalized, and given penicillin for three days. Blood cultures were negative and recovery was complete without evidence of cardiac embarrassment. She was discharged on the ninth day after admission and was again followed in the cardiac clinic until the eighth month when readmission was advised because of mild pre-eclampsia. The cardiac status had remained unchanged. The patient remained in the hospital on a toxemia regimen and improved. She had a normal spontaneous delivery under open-drop ether, after eight hours of labor at term. The baby weighed 3,420 Gm. The pulse and respirations remained normal throughout labor. The blood loss at delivery was measured at 100 c.c. Penicillin was given for five days. Because of the age and parity and development of eyeground changes, tubal ligation was performed under gas-oxygen-ether anesthesia on the fourth postpartum day. Recovery was uneventful and mother and baby were discharged well on the thirteenth postoperative day. Follow-up examination six months later revealed no change in the cardiac status.

CASE 3.—C. L. Subacute bacterial endocarditis in May, 1945. Blood cultures showed *streptococcus viridans* sensitive to 0.04 units of penicillin per c.c. The patient received ten million units of penicillin over thirty-three days and recovered. All subsequent blood cultures were negative. She became pregnant seventeen months later and was admitted for study in the third month of gestation. X-rays, electrocardiogram, circulation time, vital capacity (3,600 c.c.), and exercise tolerance were normal. The functional classification was 1B. Pregnancy was allowed to continue and the patient was discharged to be followed in the antepartum cardiac clinic. Because of obesity, she was placed on a 1,200 calorie diet. Pregnancy was entirely uneventful and admission was advised for observation several weeks prior to the expected date of confinement. Digitalis was not given. The patient had a normal spontaneous delivery under open-drop ether after an eighteen hour labor at 42 weeks' gestation. The baby weighed 3,610 Gm. The pulse and respirations remained normal throughout labor. The blood loss at delivery was measured at 350 c.c. Penicillin was given for three days postpartum and the puerperium was normal. Mother and baby were discharged well on the tenth postpartum day. Follow-up examination six weeks later revealed no change in the cardiac status.

CASE 4.—F. J. The patient was seen in the fourth month of pregnancy at which time studies revealed cardiac enlargement, electrocardiographic evidence of myocardial damage, impaired vital capacity (2,300 c.c.), and decreased exercise tolerance. The functional classification was 3C. Pregnancy was allowed to continue, since gestation was too far advanced for vaginal interruption and hysterotomy seemed ill advised. The patient left the hospital against advice and re-appeared in the fifth month with a history of upper respiratory infection, chills, fever, and weakness. Examination revealed evidence of cardiac failure, petechiae, splenomegaly, and marked anemia. Blood cultures revealed *streptococcus viridans* and a diagnosis of subacute bacterial endocarditis was established. The organism was sensitive to 0.175 units of penicillin per c.c. The patient received a total of ten million units of penicillin over twenty-eight days and recovered, all subsequent blood cultures being negative. Digitalis was given; sodium, fluid, and activity were limited, and the cardiac status improved markedly. Two small transfusions were given. The patient remained in the hospital and was delivered by midforceps under local anesthesia, after a prolonged labor of fifty-eight hours at term. The baby weighed 3,590 Gm. During labor, the pulse reached 126 and the respirations 32. The upright position in an oxygen tent was maintained throughout labor and delivery and immediately postpartum. The blood loss at delivery was measured at 200 c.c. Penicillin was administered during labor and the first week post partum. The cardiac status improved after delivery and the patient and baby were discharged well three weeks later. Therapeutic abortion of a two months' pregnancy was performed one year later at which time the cardiac classification was 3C.

sterilization is frequently performed at the time of hysterotomy. Associated pelvic pathology may occasionally favor interruption and sterilization by hysterectomy. Interference is withheld if the patient has reached the fifth month and she is carried to term anticipating the spontaneous improvement in the last month of pregnancy. The very exceptional patient, with a tight mitral valve, may become progressively worse and die undelivered. It has been suggested that late hysterotomy might avert this fatal outcome, but the impression is gained that, under ideal conditions of care, this situation will rarely be encountered. There is great risk in discharging the patient from the hospital once cardiac failure has occurred antepartum, even though she may have completely recovered from the episode of failure. The mortality in Class 4 is about 15 per cent.

Sodium, fluid, and activity are restricted. Cardiologists have recently stressed that it is unnecessary to limit fluids if sodium is curtailed. It is practically impossible, however, to give an adequate pregnancy diet without at least two to three grams of sodium, and, for this reason, we have insisted on the limitation of fluids. Anemia and obesity should be corrected to remove extra cardiac work. If digitalis has not already been required, it is frequently started in the last trimester, in anticipation of the peak of the cardiac burden. In some instances, the Class 3 patient may have been discharged and closely followed on the same regimen in the cardiac clinic. Sexual relations are interdicted. Re-admission is usually advised at the height of the circulatory burden. Oppel⁷ has shown that serious upper respiratory infections may precipitate decompensation. Therefore, hospital treatment is recommended in the event of a bad cold or bronchitis, and penicillin is given to prevent subacute bacterial endocarditis. Antibiotics are also given in the event of other serious infection, or dental extraction.

The unsatisfactory obstetric and cardiac results which followed induction of premature labor led to the use of cesarean section for premature delivery. Knowledge of the late physiologic amelioration of the cardiac burden led to the abandonment of any type of premature interference but until recent years the trend to abdominal delivery persisted. Whereas patients with rheumatic heart disease did not tolerate the usual desultory labor produced by premature induction, it has since been shown⁸ that they do tolerate the more satisfactory type of labor which occurs spontaneously at term. In fact, vaginal delivery has been shown to be safer than abdominal delivery. This does not imply that cesarean section should not be performed in a cardiac with an obstetric indication such as placenta previa, cephalopelvic disproportion, dystocia labor, etc., but it does mean that cesarean section is seldom if ever indicated because of the rheumatic heart disease per se. The vast majority of patients can be successfully delivered by the vaginal route and the hazards of labor reduced with continuity of treatment including careful functional evaluation, good antepartum care, adequate digitalization, and shortening of the second stage of labor. Brown and her associates⁹ have suggested that vaginal delivery is better tolerated than cesarean section because the repeated uterine contractions of labor prepare the

CLASS 3.—Patients with cardiac disease and marked limitation of physical activity. They are comfortable at rest. Discomfort in the form of undue fatigue, palpitation, dyspnea, or anginal pain, is caused by less than ordinary activity.

CLASS 4.—Patients with cardiac disease who are unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency, or of anginal syndrome, are present, even at rest. If any physical activity is undertaken, discomfort is increased.

As the functional capacity does not always determine the amount of physical activity which should be permitted, the following "Therapeutic Classification" is added as a guide to management:

CLASS A.—Patients with cardiac disease whose physical activity need not be restricted.

CLASS B.—Patients with cardiac disease whose ordinary physical activity need not be restricted, but who should be advised against unusually severe or competitive efforts.

CLASS C.—Patients with cardiac disease whose ordinary physical activity should be moderately restricted, and whose more strenuous habitual efforts should be discontinued.

CLASS D.—Patients with cardiac disease whose ordinary physical activity should be markedly restricted.

CLASS E.—Patients with cardiac disease who should be at complete rest, confined to bed or chair.

Hamilton and Thomson⁶ prefer to classify patients as "favorable" or "unfavorable," the latter including those with history or signs of congestive failure, dangerous disorder of the heartbeat, or serious complicating disease. Twenty per cent of the "favorable" cases revert to "unfavorable" during the course of pregnancy.

We have gained considerable prognostic confidence in the classification of the New York Heart Association. Experience has shown that the vast majority of Class 1 and Class 2 patients go through pregnancy and labor without serious cardiac difficulty, and they are followed in the special antepartum cardiac clinic by an obstetrician and cardiologist.

Class 3 and Class 4 patients constitute about 15 per cent of all cardiacs and they present the real problems in management. Admission is advised at the first visit, and cardiac measures are prescribed as indicated until compensation has been satisfactorily restored. The cardiac burden was formerly thought to increase progressively throughout gestation and it was common practice to interrupt pregnancy in the second or third trimester. We have since learned that the cardiac burden begins to rise significantly about the fifth month and reaches a peak in the last trimester, with definite amelioration in the last month. If pregnancy is less than five months advanced, and provided the patient agrees, interruption may be performed by vaginal therapeutic abortion, or abdominal hysterotomy, depending upon the size of the uterus. It may also be justifiable to interrupt early pregnancy in patients, who, despite adequate current cardiac reserve (Class 1 or Class 2), may have recovered from subacute bacterial endocarditis during the preceding six months. The cardiac reserve may possibly change, due to delayed valvular damage incident to the healing process. Tubal

with congenital heart disease¹³ is essentially the same as that for rheumatic cardiac patients. The majority with serious congenital heart disease succumb before reaching puberty. Cyanosis per se is not a contraindication to pregnancy. The dangers of a venoarterial shunt must be kept in mind. Coarctation of the aorta was found to present a special problem for, in this unusual condition, the functional classification is not necessarily related to the immediate prognosis because of the ever-present danger of rupture of the pathologically thinned aorta or cerebral vessels. A study of 29 cases of this condition showed that about half the patients suffered a deleterious effect from childbearing. Five died during pregnancy or shortly after delivery (two from rupture of the aorta, one from cerebral accident, one from cardiac failure, and one from endocarditis). Ten patients, surviving pregnancy, were definitely made worse by it. It was felt that pregnancy and labor presented such risks to patients with coarctation of the aorta that therapeutic abortion may be indicated or delivery by cesarean section advised.

Subacute Bacterial Endocarditis During Pregnancy.—There is insufficient evidence to date, to suggest that the development of subacute bacterial endocarditis during pregnancy significantly alters the management of pregnancy, delivery, or the puerperium, as outlined above. Fever accompanying the illness might induce abortion or premature labor. Case 4 carried to term despite a transient febrile course. Whereas Case 5 delivered prematurely, she had delivered at the same period of gestation in her previous pregnancy.

The fear that pregnancy may exert an unfavorable influence on the course of subacute bacterial endocarditis has already been mentioned. The incidence of heart failure complicating the disease might be increased due to the added burden of pregnancy. Regardless of the extra load imposed, it would appear inadvisable to interfere during the acute phase of the disease. Once the disease is under control, anticipation of subsequent valvular damage incompatible with pregnancy might justify interruption of early gestation despite adequate current cardiac reserve. The pathologic end result of this valvular healing process is too unpredictable, however, to warrant interruption after the fifth month of pregnancy. Future experience may have to alter this attitude.

Pregnancy should not alter the treatment of subacute bacterial endocarditis. Just as in the nonpregnant patient, it is important to determine the offending organism and its penicillin sensitivity, and render adequate dosage. The *streptococcus viridans* is the most common etiologic agent. Other organisms which occasionally cause subacute bacterial endocarditis are hemolytic and anhemolytic streptococci, staphylococci, *Hemophilus influenzae*, *Brucella melitensis* and others. Mixed infections also occur. Streptomycin is at present the antibiotic of choice for penicillin-resistant streptomycin-susceptible organisms.

Loewe and Eiber¹⁵ recently reported eleven cases of clinically authentic subacute bacterial endocarditis (past history of rheumatic or congenital heart disease, fever, lassitude, weakness, anorexia, cutaneous or visceral embolization, and splenomegaly) in whom blood cultures were sterile despite repeated efforts. One case revealed organisms in the histopathologic sections at autopsy but no

cardiovascular system for permanent occlusion of the placental circulation by gradual diminution of total blood volume. The uterine contractions diminish arterial inflow to the placenta and increase the outflow causing small auto-transfusions. These theoretically produce transient rises in the venous pressure and capillary filtration decreases the total blood volume.

The pulse and respiratory rates intrapartum provide a valuable guide to the cardiac status, for it has been observed^{10, 11} that elevation of the pulse rate above 110 per minute with a respiratory rate above 24 per minute, or such elevation of the pulse rate alone during the first stage of labor, preceded each instance of intrapartum or postpartum heart failure by a long enough period to provide ample warning of its approach. Conversely, 50 per cent of patients displaying this reaction went on to decompensation. Accordingly, any patient showing these pulse and respiratory rates during the first stage of labor should be rapidly and completely digitalized if this has not already been accomplished. She should be kept upright in bed, given oxygen, and delivered as soon as feasible after full cervical dilatation to avoid the bearing down efforts of the second stage of labor. The upright position and oxygen should be maintained throughout delivery and at least the first twenty-four hours post partum. In the event of frank decompensation, atropine, aminophylline, and bloodless tourniquet phlebotomy are employed. Analgesia is used during labor as indicated but restlessness and excitement are avoided. Local anesthesia or open-drop ether is safest for delivery. The drop in blood pressure which may accompany caudal block or spinal anesthesia makes these agents undesirable. Whereas cyclopropane allows for the administration of relatively large oxygen concentration, this anesthetic is contraindicated because of its tendency to produce cardiac arrhythmias. The incidence of spontaneous abortion and premature labor, the infantile mortality, the duration of labor, and the blood loss at delivery, in women with serious rheumatic heart disease, are not significantly different from values in normal women.⁸ Early puerperal ambulation is encouraged as soon as the cardiac status warrants. Breast feeding is not advocated because of increased physiologic demands and dangers of mastitis.

Wheeler¹² found evidence of a precipitating factor in 54 of 200 cases of subacute bacterial endocarditis. Nine of these were ascribable to abortion or delivery, such causes being second in incidence only to upper respiratory infection. Accordingly, we have advocated the prophylactic use of antibiotics during labor and the puerperium. If sulfonamides are also administered, care should be exercised in the concomitant use of large amounts of soda bicarbonate to prevent crystal formation. If bicarbonate is given in the recommended ratio of 4 Gm. to 1 Gm. of sulfonamide, fluid retention may develop to a dangerous degree.

The cardiac regimen as outlined above requires all the skill and niceties of medical and surgical obstetrics, and only when these are available should one feel justified in assuming the responsibility for pregnancy complicated by serious rheumatic heart disease.

We have had no experience with subacute bacterial endocarditis in congenital heart disease during pregnancy, but the obstetric management of patients

the valvular pathology has resolved. The advisability of childbearing should then be determined by the current cardiac status, and accepted concepts of the management of the underlying rheumatic or congenital heart disease followed as outlined during pregnancy, delivery, and the puerperium. The type of delivery should be determined primarily on obstetric indications.

2. There is insufficient evidence to date, to suggest that the development of subacute bacterial endocarditis during pregnancy significantly alters this same management. Anticipation of delayed valvular damage may justify interruption of early pregnancy despite current adequate cardiac reserve.

3. Pregnancy does not alter the treatment of subacute bacterial endocarditis. The antepartum use of anticoagulants may endanger the fetus. Normal blood coagulation values should not be disturbed at the time of delivery or in the early puerperium.

4. The prophylactic use of antibiotics during labor and the early puerperium may prevent the development or recurrence of subacute bacterial endocarditis in patients with rheumatic or congenital heart disease.

The author is indebted to Dr. Curtis J. Becker of Staten Island, N. Y., for his cooperation in the management and delivery of Case 1.

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organisms could be recovered from the thrombocleerative endocardial lesions. The authors conclude that cases with clinically authentic subacute bacterial endocarditis should be treated promptly and intensively, as though they had positive blood cultures. The diagnosis usually resolves itself within one week: if the patient has subacute bacterial endocarditis, there is appreciable clinical improvement accompanied by recession in temperature; if, however, the patient should have acute rheumatic fever (which presents the main diagnostic problem) the clinical manifestations remain static or may, in fact, become aggravated. Mention has already been made in this paper of two cases in which the diagnosis of subacute bacterial endocarditis was made clinically without positive blood cultures and penicillin started during pregnancy with subsequent cure. Both patients survived pregnancy and delivered living children.

Anticoagulant and antibiotic therapy have been combined in an attempt to decrease the incidence of embolic complications. Serious hemorrhagic manifestations have occurred (as in Case 5), and the end results of combined therapy have not been superior to those of antibiotic therapy alone. Labate¹⁶ reported a case of antepartum thrombophlebitis treated with dicumarol for fifty-one days. The baby died in utero, and autopsy revealed massive mediastinal hemorrhage which could not be accounted for except by the dicumarol administered to the mother ante partum. Serious hemorrhage may result from disturbance of the normal clotting mechanism during labor and the early puerperium. The hazards of anticoagulant therapy at these times is apparent. Furthermore, Moore¹⁷ has shown that the valvular lesions in subacute bacterial endocarditis are not of thrombic character, and he concluded that there was no pathologic basis for the use of anticoagulants in the disease.

Summary

There have been 10 cases with a diagnosis of subacute bacterial endocarditis complicating pregnancy in some 50,000 patients at the New York Lying-In Hospital from 1932 through 1947. The incidence of this complication is 0.02 per cent. Three cases with positive blood cultures occurred before the use of penicillin and all died during pregnancy or the puerperium. Seven cases treated with penicillin survived pregnancy and delivered normal living children. Two of the penicillin-treated cases had clinically authentic subacute bacterial endocarditis during pregnancy unconfirmed by positive blood cultures. Five of the penicillin-treated cases were proved by positive blood cultures: three had recently recovered from the disease prior to the pregnancy under consideration, and two developed the disease during pregnancy. The five proved cases are reviewed in an attempt to evaluate the significance of subacute bacterial endocarditis prior to and during pregnancy. An outline for the management of pregnancy, delivery, and the puerperium in rheumatic and congenital cardiac patients is given.

Conclusions

1. The past history of subacute bacterial endocarditis is not necessarily a contraindication to subsequent pregnancy. Pregnancy should be deferred until

Using the technique of uterotubal insufflation, extensive studies have been made on the oviducts of the rabbit. The correlation of the rhythmic tubal contractions in relation to the hormonal state has been studied and the effects of various drugs have been demonstrated. Wimpheimer and Feresten⁹ demonstrated the functional changes in castrated rabbits, rabbits primed with estrogens alone, and later with progesterone. Castration was followed by marked reduction in the frequency and amplitude of the tubal contractions. The contractions could be restored to normal patterns by the administrations of estrogens. Rubin and Davids¹⁰ demonstrated the striking changes in tubal activity occurring with the administration of testosterone propionate. This hormone had an inhibiting effect on the tubal musculature, greatly diminishing its general tonicity and the amplitude of its contraction. The effects of Pituitrin, adrenergic and cholinergic drugs on the Fallopian tube in relation to the hormonal status was studied by Davids and Bender.¹¹ The hormonal state strikingly affected the tubal response to the various drugs administered.

In the human being, cyclic variations in tubal activity were found by Rubin,¹² using uterotubal insufflation clinically. Daily insufflations were undertaken by Sharman¹³ on one patient throughout a menstrual cycle. He concluded from this case that there was no material change in the type of tracing obtained during any phase of the menstrual cycle. In this particular report, Sharman makes no mention of the correlation of the tubal activity with accurate knowledge of the ovarian activity by endometrial biopsy, vaginal smears, or basal temperature curves.

Methods

In the present clinical investigation, an attempt is made to correlate the Fallopian tubal activity in patients with normal ovulatory menses and patients who have repeated anovulatory bleeding. The effects of hormonal administration were studied in a number of cases. The patients were selected from those attending the sterility and endocrine clinics, where they had had comprehensive medical studies. Each case selected had essentially normal genitals, with no palpable uterine or tubal pathology. Basal temperature charts were kept accurately over a number of months by each subject. Repeated endometrial biopsies were performed, to determine the type of menstrual bleeding before and during the period of tubal study. The insufflation apparatus used was the standard Rubin model made by Becker.

All physical factors in the machine were kept constant throughout the tests. The gas was delivered under a pressure of 15 pounds and at a constant rate of flow of 60 c.c. of carbon dioxide per minute. The pressure and rate of flow were checked each day before starting any tests. The insufflations were performed by one person in order to eliminate any variations in technique and to establish satisfactory cooperation between patient and doctor. The cervix was exposed, cleansed, and painted with 3½ per cent iodine. It was then grasped with a tenaculum and a canula introduced into the cervical canal. A few moments were allowed to pass, until the patient was quiet and at ease, before the flow of gas was started. Proper air-tight obturation of the cervix was obtained by slight pressure of the rubber acorn tip of the canula against the cervix and slight traction upon the canula. Care was taken not to displace the uterus from its normal position in the pelvis. Such a procedure can possibly

FALLOPIAN TUBAL MOTILITY IN RELATION TO THE MENSTRUAL CYCLE

Clinical Study With Kymographic Uterotubal Insufflation

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THE hormonal activity of the ovary produces definite morphologic and functional changes in the uterus and Fallopian tubes. The effects on the uterine musculature and endometrium have been repeatedly demonstrated by many investigators. The relationship between the cyclic hormonal activity of the ovary and the functional state of the Fallopian tube in the human being has not been so clearly established.

Moreaux,¹ in 1913, investigated the changes occurring in the tubal mucosa of the rabbit. He found that the tubal mucous membrane was lined with ciliated epithelium during the sexually quiescent period. During the heat periods and early gravidity the ciliated lining of the tube was transformed into a secreting structure and the tubal lumen filled with granules of secretion. Structural changes of the same nature were demonstrated in the dog by Courier and Gerlinger² and in the human tubal mucosa by Westman,³ Snyder,⁴ and others. The cellular transformation is controlled by the ovary and castration prevents these changes.

The spontaneous contractions of the uterine and tubal musculatures are also regulated by the ovarian hormones. In 1922, Blair⁵ and Seekinger⁶ independently demonstrated the cyclic activity in the musculature of the genital tract. Blair first observed this phenomenon in the excised uterus of the rat. Spontaneous contractions were slowest at estrus, the rate increasing gradually to a maximum in the resting stage. Wilson and Kurzrock⁷ many years later established the normal pattern of human uterine motility in relation to the menstrual cycle. Seekinger studied the contractions of the excised Fallopian tube of the pig. He found uniform contractions occurred four to six times a minute except during estrus, when the contractions occurred ten to fifteen times a minute with alternation of groups of small and large excursions. The increased rapidity and large amplitude of contractions coincide with the time of Graffian follicle rupture and the passage of the ova through the tube. Studies in other species verify the relationship of ovarian function and spontaneous activity.

Uterotubal insufflation as a clinical test for tubal patency was introduced by Rubin⁸ in 1920. It was not until 1925, however, that he obtained kymographic recordings of the tubal contractions. By this means, the functional activity of the intact Fallopian tube can be studied accurately in the human being as well as in the experimental animal. The correlation of preoperative kymographic tracings and the genital pathology demonstrated at the operating table and in the pathologic laboratory has greatly increased the value of the clinical test. The study of repeated kymographic curves in any given patient affords accurate knowledge of the functional state of the tube as well as a good impression of the pathologic conditions which may exist.

lished usually between levels of 20 to 50 mm. Hg. The patterns of tubal contractions showed no significant change throughout the entire menstrual cycle. The contractions occurred four to five times a minute and their amplitude was 5 to 10 mm. Hg. The kymographic tracings from day to day were quite similar. As a group, the base level at which contractions occurred was lower than that of the normal ovulatory group. In one case, tubal contractions were absent throughout the test period. This case will be more fully discussed later. (Fig. 2.)

pat. E.V., AGE 23, L.M.P 8-21-46.

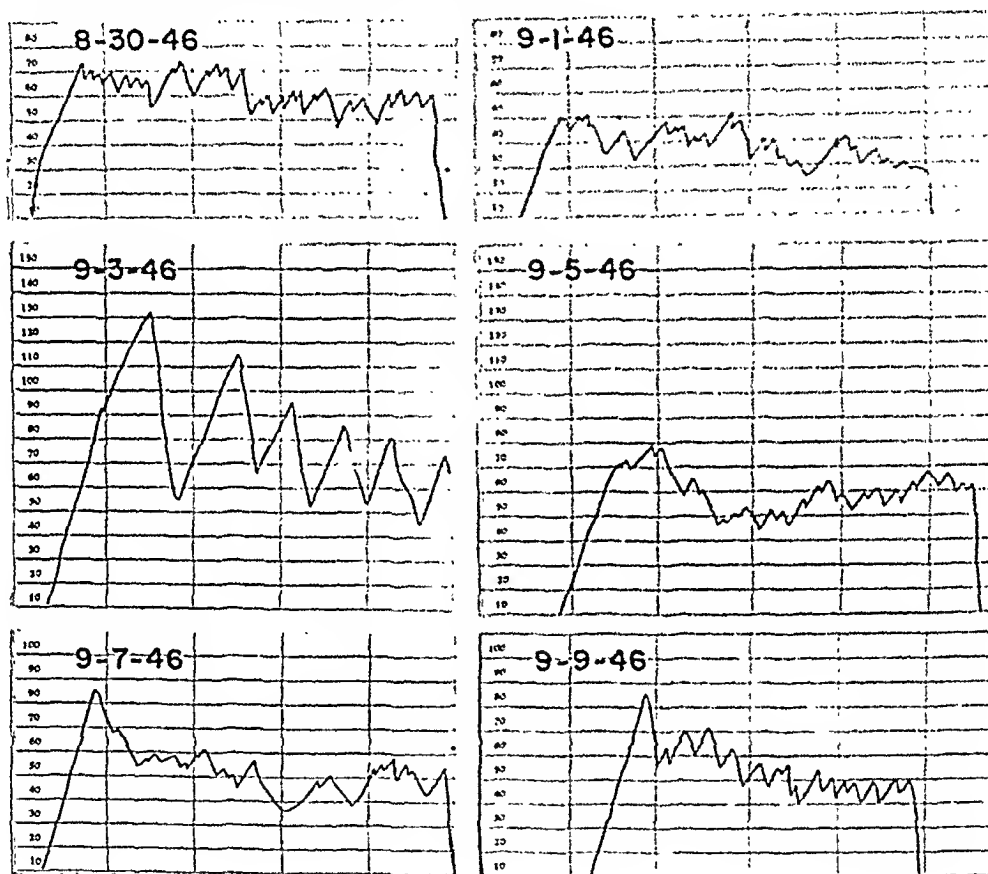


Fig. 1.—Above are six of the eleven consecutive tubal insufflation curves obtained on a patient during a normal menstrual cycle. These curves were obtained on the 10th, 12th, 14th, 16th, 18th and 20th days of the cycle. A marked change in tubal motility is seen on the 14th day of the cycle (9-3-46) which coincided with a distinct rise in the patient's basal temperature curve. Endometrial biopsy on the first day of the menses revealed a secretory endometrium.

The effect of estrogens on the pattern of tubal motility was studied in five women with normal ovulatory menses and in three women with anovulatory menses. In the latter cases, estrogens alone and in combination with progesterone were given. Stilbestrol was given in doses of 1 mg. daily and, in some cases, increased to 2 mg. daily. In the five normally menstruating women, the stilbestrol was started on the tenth day following the onset of the menses. In four of these cases, there was no appreciable change in the character of the daily tubal pattern. In one case, however, a very striking alteration took place. This patient had been insufflated on ten occasions before the administration of stilbestrol. Tubal patency had been present at pressure levels between 70 to 120 mm. Hg during these tests and the tubal contractions were of a normal

stretch the mesosalpinx and tube, giving anomalous kymographie tracings. The insufflation was performed for five minutes or more at each test.¹ The patients were insufflated every other day, starting within a day or two after the cessation of the menses. An endometrial biopsy was taken on the first day of flow of the following menstrual period. Each case was followed throughout an entire menstrual cycle and, in many cases, through two successive menstrual cycles. Certain patients with ovulatory menses were selected to determine the effect of estrogens on the tubal contraction patterns. Several patients with repeated anovulatory menses were used to test the reaction to the administration of combined estrogens and progesterone.

Material

Twenty patients with regular menses, on whom repeated endometrial biopsies revealed a secretory endometrium, were studied. The basal temperature curves exhibited characteristic temperature rises with persistent elevation of temperature until the onset of the succeeding menses. After studying the consecutive kymographie tracings obtained over the course of the menstrual cycles, certain facts became apparent. The initial pressure at which patency of the tube occurs shows marked variations from case to case in patients with normal genitals and normal menses. In individual patients the level of pressure at which patency occurs may be fairly constant throughout the cycle with only a difference of 10 to 20 mm. Hg throughout.

In other patients, the patency level occurred at times as low as 40 mm. Hg and on subsequent tests as high as 190 mm. Hg. There did not seem to be any consistent change of the tubal patency level with the time of the menstrual cycle. The majority of patients showed patency at levels between 40 and 100 mm. Hg. Of this group, only one case showed a consistently low patency level, which occurred between 10 and 30 mm. Hg throughout the test period.

The pattern of tubal contractions, that is, their frequency and amplitude, did, however, show interesting changes during the menstrual cycle. These patterns were not absolute, but occurred with sufficient regularity to permit of definite conclusions. During the first half of the menstrual cycle the contractions occurred with a frequency of four to five a minute and the amplitude of the contractions was 5 to 10 mm. Hg. During the mid-cycle, and approximately at the time of the elevation of the basal temperature, distinct changes in tubal motility were seen. The contractions appeared much less frequently, only one to three per minute, and the amplitude was greatly increased. The amplitude in some cases was increased from the previous 5 to 10 mm. Hg to levels as high as 50 mm. Hg, the average being 10 to 20 mm. Hg. This change of pattern was transient, lasting from one to two days. Following this, the contractions again occurred three to five times a minute with amplitudes of only 5 to 10 mm. Hg. The contractions were less regular and the base level of contractions was usually somewhat lower than during the early phase of the cycle. The general pattern of contractions showed no remarkable change from that of the early phase. (Fig. 1.)

Five patients whose menses were irregular and on whom repeated endometrial biopsies revealed proliferative endometrium were studied. Their basal temperature curves showed no characteristic changes such as are associated with the ovulatory cycle. These patients were insufflated in the same manner as the previous group. The average pressure level of tubal patency was somewhat lower than that found in the normal ovulatory group. Patency was estab-

Ten days later the insufflation test was repeated. Patency was present at 40 mm. Hg and tubal contractions were of normal character, the frequency being five to six per minute and the amplitude 5 to 10 mm. Hg. Seven subsequent insufflation tests revealed tubal patency at pressure levels between 20 and 60 mm. Hg and contractions remained regular at five to six per minute with amplitudes of 5 to 10 mm. Hg. (Fig. 4.)

pat. D.B., AGE 24, L.M.P 3-10-46.

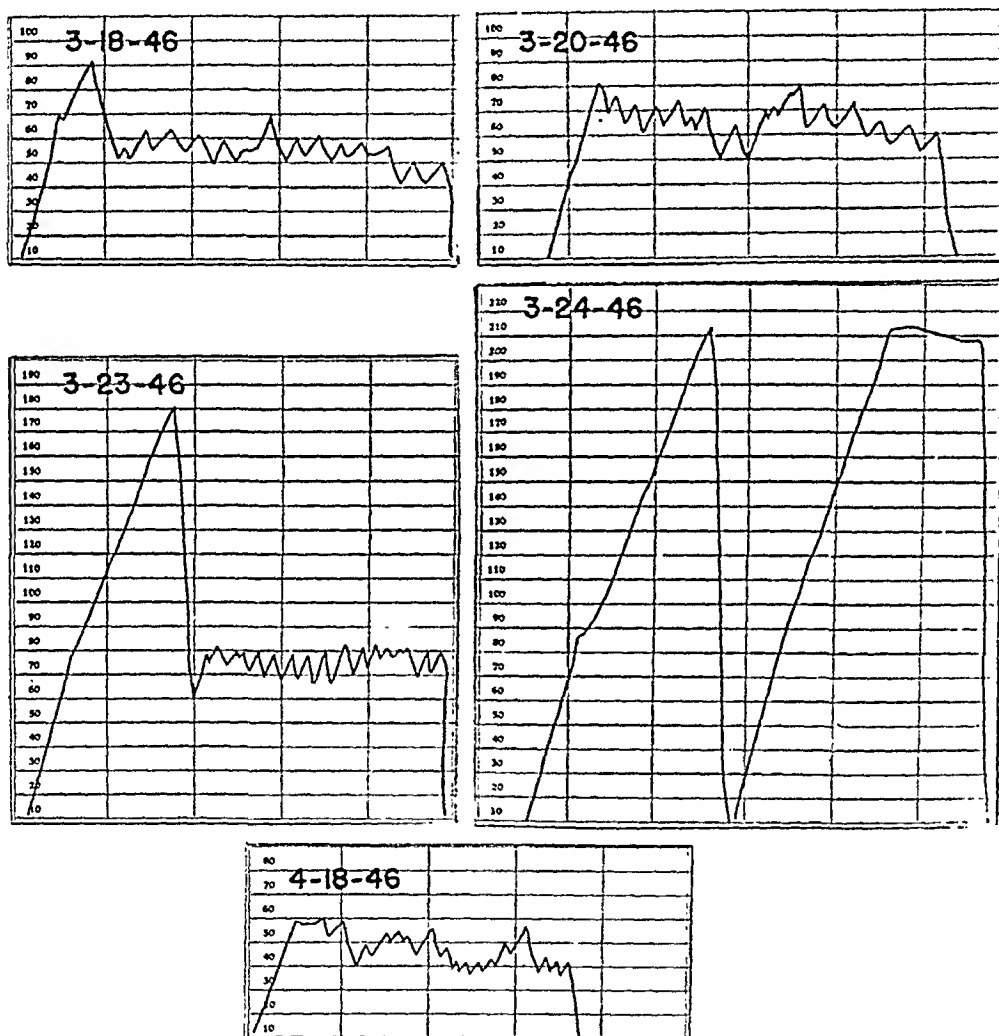


Fig. 3.—The above graphs demonstrate the effect of the daily administration of 1 mg. of stilbestrol to patient D. B., starting on the 9th day of her menstrual cycle. After five days (3-23-46) on stilbestrol, the tubal patency level rose to 180 mm. Hg. On the 6th day (3-24-46), patency could not be established at pressures as high as 210 mm. Hg. Four subsequent tests during the next eight days revealed nonpatency at pressures of 200 mm. Hg. Medication was stopped on the first day of the menses and ten days later (4-18-46) tubal patency was present at 60 mm. Hg and a normal pattern of tubal motility was present.

In three of the anovulatory cases, stilbestrol and progesterone were given in combination. The dosage was 1 mg. of stilbestrol daily in combination with 50 mg. of oral progesterone. Each patient received 10 mg. of progesterone by injection three times a week. In two of the three patients, the endometrial biopsies at the next menses revealed a secretory endometrium for the first time. In the third patient, the endometrium was still in the proliferative phase.

pattern. After five days of medication, 1 mg. stilbestrol daily, the patency level rose to 180 mm. Hg and on the sixth day the pressure rose to 200 mm. Hg without establishing tubal patency. Over the next eight days, four tests were performed and each time the pressure elevation was 200 mm. Hg corresponding to that encountered in the case of closed tubes or marked uterotubal spasm. The patient had a normal period the day following the last test and stilbestrol was stopped. The endometrial biopsy revealed a secretory endometrium. Ten days after the cessation of stilbestrol administration, an insufflation test was again performed. Tubal patency was present at 80 mm. Hg and the pattern of tubal contractions was normal. Two repeated tests during this same month revealed patency at normal pressure levels with normal tubal motility. (Fig. 3.)

pat. M.M., AGE 26, L.M.P. 5-9-46.

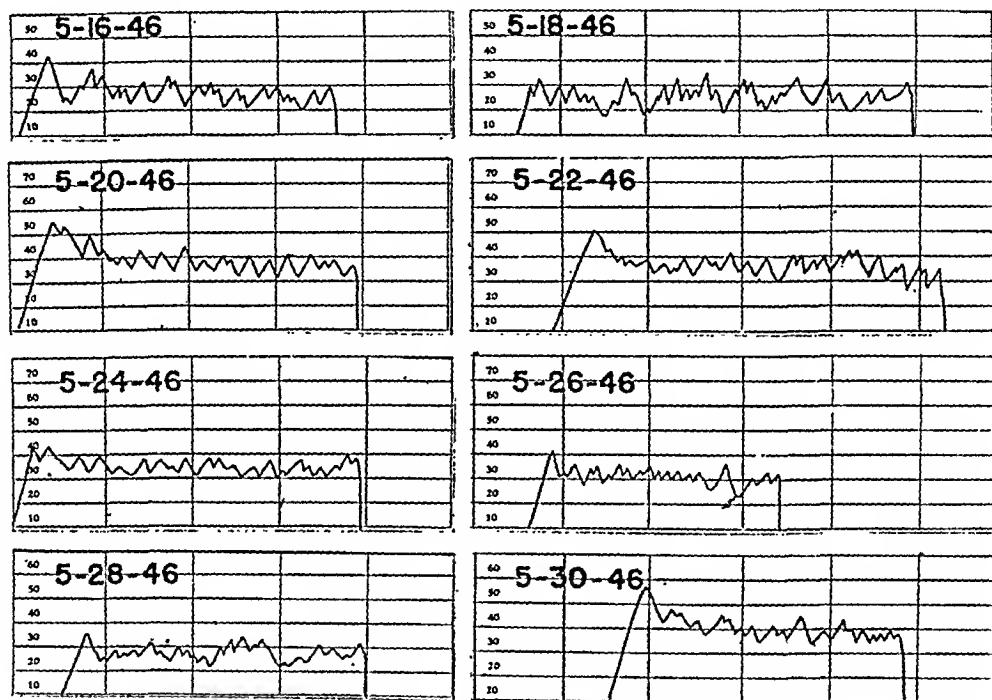


Fig. 2.—These eight consecutive uterotubal insufflation curves were obtained from a patient who had repeated anovulatory menses. The curves are quite similar from day to day. There is no marked change in motility on any day such as seen during the ovulatory menses in Fig. 1. Endometrial biopsy performed on the first day of the menstrual flow revealed a proliferative endometrium.

In the three patients with anovulatory menses, 1 mg. of stilbestrol was given daily following the cessation of the last menstrual period. One patient showed no appreciable change in the tubal pattern throughout the test period. A second patient showed only a slight increase of 20 to 30 mm. Hg in the pressure level of tubal patency. The third case, however, exhibited a very marked alteration in the kymographic tracings. This patient had had eight insufflation tests performed before starting stilbestrol medication, 1 mg. daily. Tubal patency was present at 50 to 90 mm. Hg and tubal contractions were absent, the curve being a slightly irregular line. This type of tracing was present on all eight tests. After eight days of stilbestrol administration, insufflation revealed tubal spasm at 200 mm. Hg. This occurred on four subsequent tests and then was followed by a four-day menstrual flow. The endometrial biopsy revealed a proliferative endometrium. The stilbestrol was stopped at the onset of the menses.

not entirely controlled by the hormonal activity of the ovary. It may be induced by a physiochemical reflex to the actual process of the rupture of the ovarian follicle and the passage of the ovum through the peritoneal cavity and Fallopian tube. In the absence of ovulation, the slow contractions of large amplitude do not occur. In the patient with anovulatory menses, the artificial stimulation of the Fallopian tubes by sufficient estrogens and progesterone to produce a secretory endometrium does not produce alteration of the tubal motility to resemble that seen at ovulation in the normal patient. It is also of interest that the basal temperature curves were not affected by the administration of the hormones in such combination as to produce a secretory endometrium. The pattern of motility of the Fallopian tube and that of the uterus through the menstrual cycle show distinct differences. Except for the short period following ovulation, the tubal motility of the early and late phases of the menstrual cycle are not very dissimilar. The uterus, on the other hand, develops two distinct patterns of motility. The contractions of the early phase of the cycle being rapid, four to five per minute and of low amplitude, while the latter half of the cycle is characterized by slow large amplitude contractions occurring once or twice a minute. These slow high contraction waves persist throughout the entire luteal phase of the cycle and do not seem comparable to the large slow contractions which occur in the Fallopian tube for so short a time during the period of ovulation.

The response of the individual patient to the administration of normal doses of a drug or hormone shows great variation. This is clearly demonstrated by the two cases of the eight so treated in which 1 mg. of stilbestrol produced an elevation of pressure up to 200 mm. Hg. Whether this was due to increased sensitivity and spasm of the tubal musculature alone, or possibly also to an actual obstruction of the tubal lumen due to proliferation of the tubal mucosa, one cannot say. However, where hormones are used as a therapeutic agent in sterility, it would probably be wise to determine if the patient is having an abnormally sensitive tubal response, as was seen in the two patients discussed. Theoretically, such a response would be detrimental to the normal passage of the ovum through the Fallopian tube. In one of these cases, the kymographic tracings revealed tubal patency but a complete absence of tubal contractions. After a short period of estrogen therapy, tubal obstruction was present on repeated tests until the medication was stopped. Following the next menses, tubal patency was present and contractions assumed a normal pattern for the first time. This patient had been under observation since 1941 and at no previous time did she exhibit normal tubal motility. Rubin¹² and White¹⁴ have suggested estrogens as a therapeutic measure in cases with permeable strictures of the tubes, with the hope that such a response might occur.

It is of interest to note that in this group of twenty-five patients repeated insufflations produced no untoward reactions. Two of the patients became pregnant within two months after the studies were terminated. One was insufflated twenty times and the other eighteen times. It has been our feeling

Despite the induced change in the endometrial structure in the two cases, there was no alteration in the character of the basal temperature curves and no striking alteration in the kymographic tracings of the tubal contractions.

pat. M.J., AGE 29, L.M.P. 4-14-46

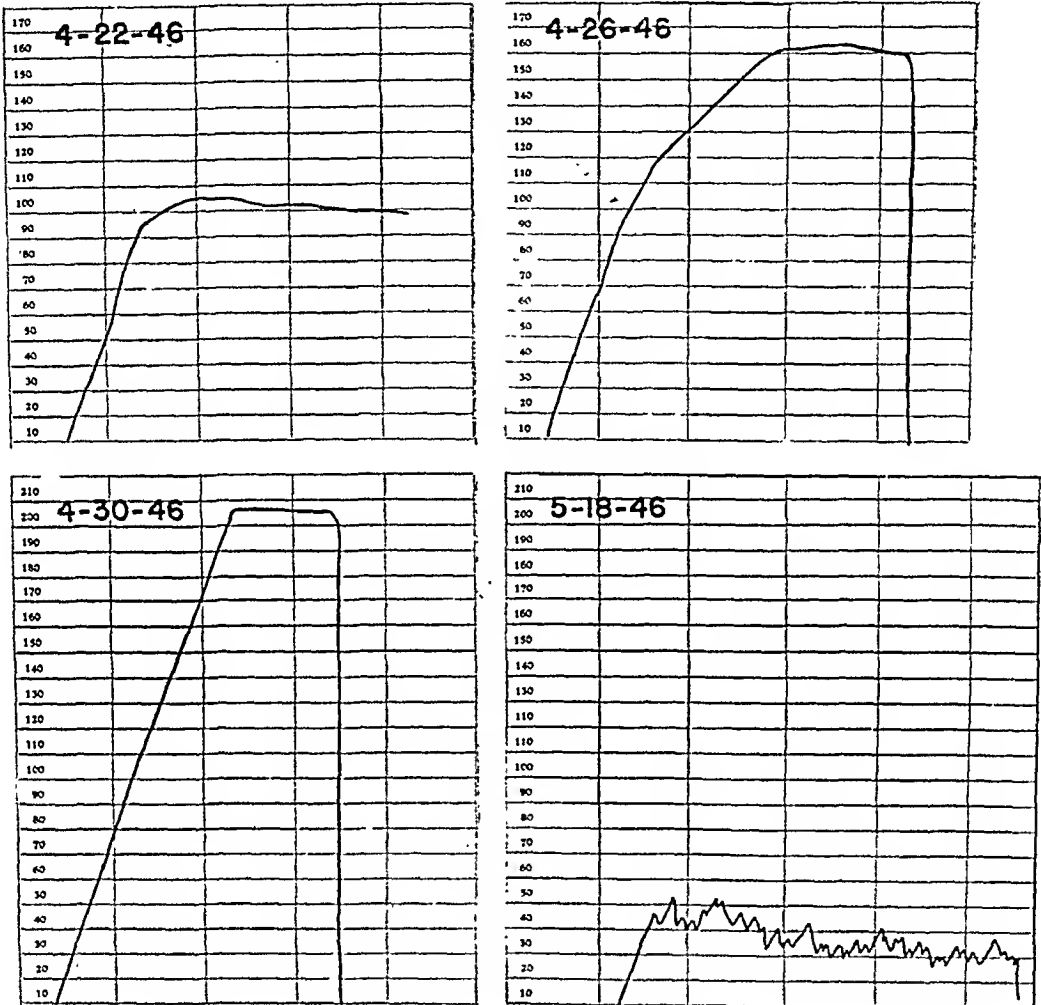


Fig. 4.—The above uterotubal insufflation curves demonstrate two striking effects of estrogen therapy. The graph of 4-22-46 shows no tubal contraction waves. This type of tubal curve was present on eight previous insufflations. Administration of 1 mg. of stilbestrol daily for four days produced a rise in the tubal patency level on 4-26-46 to 160 mm. Hg and in eight days (4-30-46) tubal patency could not be established at 200 mm. Hg. Ten days following the menses and the cessation of stilbestrol therapy (5-18-46) tubal patency was established at a pressure of 45 mm. Hg and tubal contractions of a normal pattern were seen for the first time.

Comment

The comparison of the consecutive kymographic records in the two groups of patients studied definitely establishes a difference in their functional state during the menstrual cycle. The one striking difference is that seen during the period at which we believe ovulation takes place. It is at this time, for one to two days, that the contractions of the Fallopian tubes become slower and of much greater amplitude. There is no such activity seen in those cases in which anovulatory menses occur. This change in tubal motility is probably

FAILURE OF PROSTIGMIN TO AFFECT UTERINE BLEEDING IN THE RHESUS MONKEY

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THE so-called prostigmin test for pregnancy has attracted considerable attention in recent years because of its simplicity and the high rate of success attributed to it. There are now on record dozens of reports which include hundreds of cases in which the drug has been used in the treatment of women with amenorrhea. Yet there has been reported no study of the effect of prostigmin on menstruation under controlled conditions.

The apparent ability of prostigmin to induce menstruation in the nonpregnant woman with delayed bleeding is of great interest to the student of menstrual phenomena. In the laboratory, menstruation has been induced in animals only by oophorectomy, transection of the spinal cord, and hormone withdrawal in castrates. If prostigmin is effective in initiating the breakdown processes of endometrium which result in menstruation, its mode of action is certainly diametrically opposite to that of the steroid sex hormones whose effect in producing bleeding is manifest only when they are withdrawn. Furthermore, the duration of action of prostigmin is relatively brief, and it must be assumed that its administration initiates a chain of events which completes itself without further stimulus. As will be indicated, we are at present without any information as to how this phenomenon, if it exists, may occur.

In clinical practice, the patient who complains of amenorrhea is studied to rule out the presence of general disease, either nonspecific or endocrine in nature, or local pelvic pathology which might account for the complaint. She is then given prostigmin methylsulfate hypodermically, generally 0.5 to 1.0 mg. in the form of a 1:2000 solution, once a day for three days. If this regime is not followed by menstrual bleeding, the patient is presumed to be pregnant.

So little is known of the pathogenesis of amenorrhea in women, once general disease, pelvic pathology, and pregnancy are ruled out, that there is no accurate way of reproducing the condition in the laboratory. The rhesus monkey, whose menstrual cycles in the fall, winter, and spring average twenty-eight days in duration, normally develops amenorrhea during the summer months. In the absence of any other evidences of torpor, the animals tend to have prolonged intervals in the late spring and usually cease bleeding altogether in June, July, and August. In September, or occasionally in October, the cyclic pattern of menstruation is resumed. The color of the sex skin fades during this summer amenorrhea, indicating a decreased level of estrogenic substances, but it does not fade to the extent seen in castrates. The earliest attempts to induce bleeding in

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that the passage of carbon dioxide through the Fallopian tube, even in such frequency as occurred in this study, will not induce any abnormal change in the endosalpinx.

Summary and Conclusions

1. Twenty-five patients were subjected to repeated tubal insufflations throughout one to two menstrual cycles and the type of menses determined by endometrial biopsies and basal temperature charts.

2. Patients with normal ovulatory menses exhibit slow large amplitude contractions at the time that ovulation is presumed to occur. The patterns of tubal contractions at all other times during the menstrual cycle are quite similar.

3. The patterns of tubal motility in patients with anovulatory menses are similar throughout the menstrual cycle. No such changes occur as are seen in the ovulatory cycle.

4. The administration of estrogens did not materially affect the pattern of tubal contractions except in two cases. In these two cases, the estrogen therapy produced obstructive pressures to 200 mm. Hg until the hormone therapy was stopped.

5. Repeated uterotubal insufflation with carbon dioxide did not produce any untoward effects. Two patients became pregnant shortly after having been repeatedly insufflated, in the one case twenty times and the other eighteen times.

6. Comparison of the tubal and uterine contractions throughout the menstrual cycle reveals that they do not conform to the same patterns of motility.

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0.2 c.c. Progesterone² in corn-oil solution was given in the same manner, the largest single daily dose being 0.2 c.c.

At least four animals were used in each experiment in the series of hormone withdrawal studies. While all animals in any one experiment received identical doses of hormones, approximately half of the group received prostigmin in addition at one time, and the remainder at another. In this way, variables, such as changes in diet in the colony, climatic conditions, and differences in handling, are minimized and significant results can be obtained with relatively small numbers of animals. Since the results have all been negative, the experiments have been lumped together for the purpose of presenting the data in summary form.

Observations

A. Prostigmin During Amniotin Administration.—Three castrate animals were given approximately 400 International units of Amniotin per day for twenty days. Prostigmin was given in the middle of this course of Amniotin, but in no case did bleeding occur until after withdrawal of the hormones.

Five castrate animals were given 25,000 International Units of Amniotin daily for twenty-six days, as 0.5 c.c. of a 50,000 International Units per c.c. solution. In addition, prostigmin was given on days 21, 22, and 23 of the course of hormone injection, but bleeding did not result until after hormone withdrawal.

B. Prostigmin Following Amniotin Administration.—Eight castrate animals were given approximately 400 International Units of Amniotin daily for periods ranging from eight to nineteen days in a series of nineteen experiments. In twelve instances, prostigmin was given daily for three days beginning the day after the last dose of hormone. The time of onset of bleeding was scattered from the fourth to the eighth day after Amniotin withdrawal. The greatest delay was seen in two prostigmin-treated animals, the least in one not treated with prostigmin. In general, there was no difference between the experimental and control animals in regard to time of onset or duration of bleeding.

Five other castrates were given 25,000 International Units of Amniotin daily for twenty-six days and two of them were given prostigmin on days 27, 28, and 29. The time of onset and duration of bleeding was the same in the prostigmin-treated animals as it was in the three controls.

C. Prostigmin Following Amniotin-Progesterone Administration.—Fourteen castrate animals were given approximately 400 International Units of Amniotin daily for ten days and then approximately 200 International Units combined with progesterone increasing in amount from 0.5 to 1 mg. daily for ten to twelve days. Seven of these animals were given prostigmin on each of the three days following complete hormone withdrawal. There was no significant effect on the time of onset of bleeding.

D. Prostigmin Following Amniotin-Progesterone-Amniotin Administration.—All the animals in this group of castrates were given approximately 400 International Units of Amniotin daily for ten days and gradually decreasing doses thereafter for the next ten days, down to a daily dose of 150 International Units. During the second ten days, while Amniotin dosage decreased, progesterone in doses gradually increasing from 0.5 to 1 mg. was given. On days 21 through 26, four animals received 10,000 International Units of Amniotin daily, four others 5,000 International Units and the remaining four 1,250 International Units. Bleeding did not occur in these animals until several days after the withdrawal of all hormone administration, despite the fact that two animals in each group were given daily doses of prostigmin on days 21, 22, and 23, and

monkeys with prostigmin were naturally undertaken in these spontaneously amenorrheic animals, whose condition is at least analogous to that seen in the human being. When these attempts produced no reliable evidence of prostigmin effect, attention was turned to the possibility of affecting hormone withdrawal bleeding in castrate animals with prostigmin.

Castrate rhesus monkeys, given adequate doses of estrogens for a week or longer, will respond to the cessation of this therapy with uterine bleeding of three to seven days' duration which begins five to seven days after the last dose of hormone. The minor variations in the bleeding response depend on the size of the dose, the duration of treatment, and the volume of injected material, but with any single regime of hormone administration, the time of onset of bleeding and the duration of bleeding fall within narrow limits. If, in addition to a priming course of estrogens, a course of adequate doses of progesterone is given, bleeding follows the withdrawal of that hormone within two to three days, and lasts four to six days. The variation with this regime is less than that with estrogens alone. If a full priming course of estrogens and progesterone is followed by large doses of estrogens alone, bleeding does not ensue until after cessation of the estrogens, at which time it conforms to the pattern expected if progesterone had not been given at all. This variety of patterns of hormone withdrawal bleeding in castrate animals then offers an opportunity to investigate further the possible effect of prostigmin in initiating menstruation. The effects without prostigmin are known. If prostigmin in any way influences the process of endometrial breakdown and desquamation, it might be expected to alter the pattern or time relationships of withdrawal bleeding. Despite the fact that these conditions do not reproduce human amenorrhea, it appears worth while to report that, under these controlled conditions, there is no evidence of any effect of prostigmin on uterine bleeding in the rhesus monkey.

Materials and Methods

The animals employed in this study were mature healthy female specimens of *Macaca mulatta* in the colony of the Department of Embryology of the Carnegie Institution of Washington, in Baltimore.

Throughout the experimental periods, the animals were examined for the presence of bleeding by daily vaginal lavage.

Prostigmin methylsulfate* was administered intramuscularly in the thigh in doses of 0.38 mg. (0.75 c.c. of a 1:2000 solution) except in the few instances noted. The drug was administered on three successive days except when an animal was found to be bleeding on a day when a dose was scheduled; in this event the prostigmin was omitted.

Amniotin† was administered intramuscularly in the thigh in corn-oil solution. No special effort was made to keep the amount of injected solution constant. Except for the experiments employing massive doses, in which 0.5 c.c. of corn-oil solution was used, the amount administered daily did not exceed

*The Prostigmin employed in this study was generously supplied by Hoffmann-LaRoche, Inc.

†The Amniotin in oil and progesterone in oil employed were generously supplied by E. R. Squibb and Sons.

A final group of five animals was studied in September, following amenorrhea lasting 48 to 80 days. One of these began bleeding on the second day of prostigmin administration, which was the 49th day since the onset of the last menstrual period. The other four animals did not bleed and were not pregnant.

F. Saline Administered During Spontaneous Amenorrhea in Intact Animals.—Seven intact animals, amenorrheic for periods from 39 to 66 days, were given 0.75 c.c. of normal saline solution on three successive days. One animal had a period of bleeding beginning nine days after the last dose of saline. The other animals did not bleed in the two weeks following the saline injections and were not pregnant.

G. Summary of Experiments.—Seventy experiments on castrate animals receiving hormone stimulation were carried out. Prostigmin did not induce bleeding during administration of Amniotin. When prostigmin was given following courses of Amniotin or Amniotin and progesterone, it did not accelerate or delay the expected hormone withdrawal bleeding. When given during courses of large doses of Amniotin which had followed Amniotin-progesterone priming, prostigmin did not induce bleeding, and when given after these courses of large doses of estrogen were stopped, it did not accelerate or delay the onset of bleeding. At no time did the administration of prostigmin prolong or shorten the period of bleeding.

Twenty-one experiments on animals in the process of spontaneous amenorrhea were performed. In only one group of animals, those treated in July after brief periods of delay in menstruating, did any considerable number of animals bleed following prostigmin administration. Two other animals, with more prolonged periods of amenorrhea, bled on the day after the first dose of prostigmin. None of the other animals responded to prostigmin with bleeding.

The administration of saline solution did not induce bleeding in a group of seven animals with varying periods of amenorrhea.

The dose of prostigmin employed in these experiments, 0.38 mg. or 0.75 c.c. of 1:2000 solution, is equivalent by body weight to ten to twenty times the recommended dose range for the human subject, 0.5 to 1.0 mg. With this dose a number of the animals exhibited gross muscle fibrillations within ten minutes after injection, lasting fifteen to twenty minutes. No animals became seriously ill and no serious effects were observed. Prostigmin was given in these large doses approximately 225 times.

Discussion

The prostigmin test for pregnancy was first reported by Soskin, Waechtel, and Hechter in 1940.¹⁵ They based the use of prostigmin on the cholinergic concept of the action of estrogens on the endometrium⁷ and on the hypothesis that the failure of the patient with a previously normal menstrual history to menstruate, in the absence of general disease of a nonspecific or endocrine nature, or pelvic pathology, or pregnancy, was due to a failure of the vascular supply of the endometrium. It was argued that inasmuch as estrogens were supposed to produce hyperemia of the endometrium by their cholinergic properties, the administration of a cholinergic drug should correct this vascular failure. They stated that: "In view of the large proportion of the estrous phenomena in animals which is dependent on hyperemia, it seemed likely that the role of hyperemia was probably even more important in the periodic menstrual bleeding in the human female. Considering the mechanism of this hyperemia, it would

the other two on days 28, 29, and 30. There were no differences in time of onset or duration of bleeding between the prostigmin-treated and prostigmin-untreated animals after hormone withdrawal.

E. Prostigmin During Spontaneous Amenorrhea in Intact Animals.—Twenty-two animals with varying periods of amenorrhea, ranging from 29 to 112 days since the onset of the last menstrual period, were given the routine course of three daily doses of prostigmin.

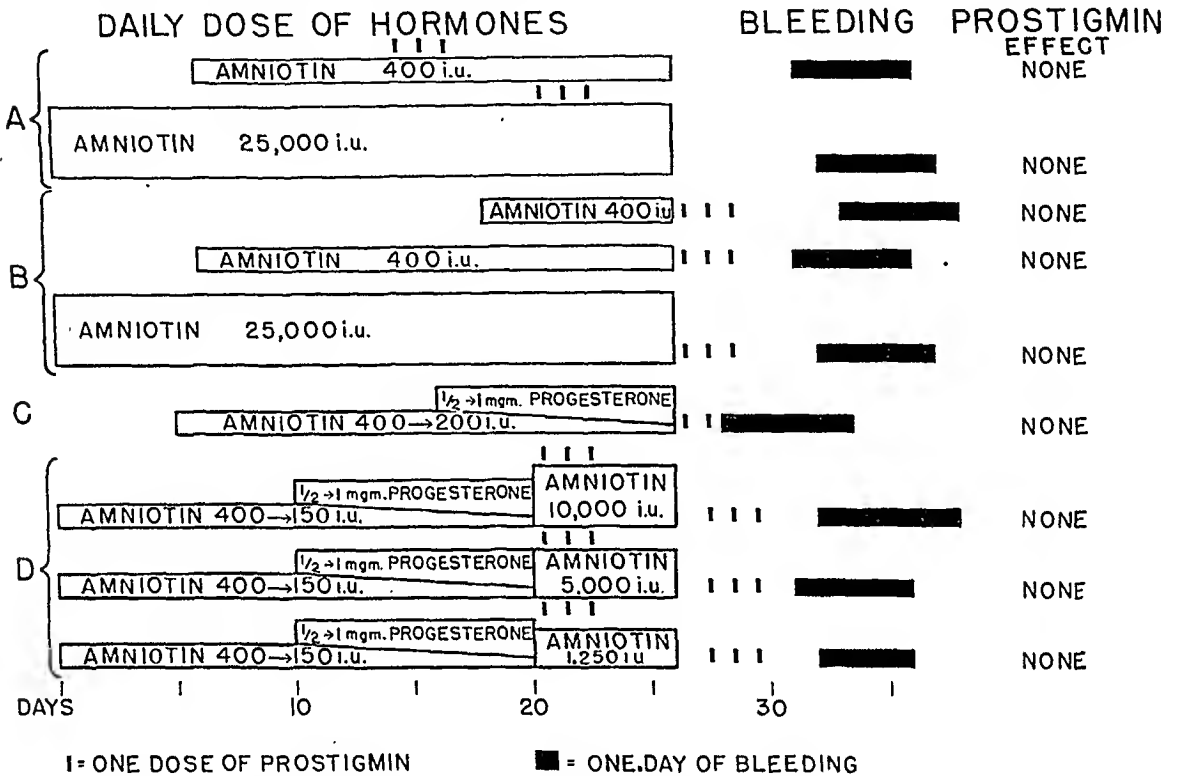


Fig. 1.—Chart of experiments designed to demonstrate prostigmin effect on hormone withdrawal in the rhesus monkey.

Experiments are grouped together as they are in the text and lettered correspondingly on the left margin of the chart. For economy of space, the days of prostigmin administration are indicated by vertical lines in relationship to each hormone regime. However, in each instance, equal numbers of animals did and did not receive the prostigmin on those days, whereas the hormone regime was the same for all in any group. The statement "None" under the heading Prostigmin Effect therefore indicates that there was no difference between the animals which did and those which did not receive prostigmin in time of onset or duration of uterine bleeding.

One group of ten animals, amenorrheic from 56 to 112 days, were given prostigmin in mid-May. One animal died of incidental causes during the experimental period. Of the remaining nine, seven did not bleed in the two weeks following prostigmin treatment. One animal bled, beginning on the day after the first dose of prostigmin, the 104th day since the last period. The other animal began to bleed on the 8th day after prostigmin was begun, the 86th day since the last menstrual period. None of these animals was pregnant.

A second group of animals was treated with 0.25 mg. daily doses of prostigmin in July. These animals had not bled for 29 to 38 days since the onset of the last menstrual period in June which, in each case, represented a greater lapse of time than was usually observed in that animal. Four of these animals bled, one on the second day and the other on the third day after completion of the course of prostigmin. In one of the latter animals only one day of bleeding was observed. None were pregnant.

twenty-four hours in a single dose, unless it acts to initiate the processes of regression in the endometrium. If this is the case, then one injection should be as efficacious as three, and the latent period of effect should be much greater than that reported by Winkelstein¹⁶ in his cases. On theoretical grounds, therefore, the prostigmin test for pregnancy can be accepted with serious misgivings if it can be accepted at all.

Virtually nothing is known of the effect of prostigmin on the reproductive systems of experimental animals. Fontana⁵ reported a few experiments in the rabbit in 1941, and recently preliminary reports of studies in the rat have appeared.² With the exception of the studies herein reported, there have been no experimental observations on primates.

Nevertheless, the great mass of reports of the use of the prostigmin test for pregnancy, most of them frankly enthusiastic, cannot be ignored. A representative but incomplete bibliography of these reports is included among the references.^{5, 6, 14, 15, 16, 17a-ab} The greatest majority of these reports consist of entirely uncritical and uncontrolled observations. For example, it is generally accepted that no known substance in therapeutic doses will induce bleeding in the normally pregnant woman. It is, therefore, not surprising that prostigmin does not do so either, yet such cases are counted as therapeutic successes. Despite the acknowledged irregularity of the human menstrual cycle, many patients who have reported themselves only one to five days delayed in the onset of menstruation have been treated and any subsequent bleeding counted as a therapeutic success. On the other hand, the patient who has previously had a normal menstrual history and now suffers amenorrhea of weeks' duration, if she is not pregnant, presumably has some serious reproductive disturbance. Many such patients have been treated with prostigmin without such essential laboratory studies as endometrial biopsy, and subsequent bleeding counted as a therapeutic success. The many instances of hysterical amenorrhea can be expected to respond well to any substitutive therapy; certainly prostigmin is no specific. However, when all such cases as these are weeded out of the reports, there remains a residuum of reports of cases which cannot be explained at the present on any basis other than the therapeutic effect of prostigmin. It is unfortunate that only two authors have included in their series of cases controls in whom placebos were used,^{6, 14} and in neither report were enough cases included to allow significant conclusions to be reached.

Amenorrhea is a normal condition in the rhesus monkey during the summer months, while the cycles in the cooler weather are approximately as regular as in the human female. When prostigmin was given to these animals exhibiting spontaneous amenorrhea, no significant number of them responded with bleeding, with the exception of one group with amenorrhea of a duration which did not fall outside the range of periods for all animals in the colony at the time of the year when the experiment was done.

In view of the failure of prostigmin to influence spontaneous amenorrhea, it was felt that attempts to influence hormone withdrawal bleeding was justified. When no effects were noted with the usual courses of estrogens and estrogen-

presumably be under the influence of at least the parasympathetic nervous system." There are, however, so many unproved assumptions in this line of reasoning that it is worth while to retrace the course of development of the concepts involved.

Pompen,¹⁰ in 1933, reported that within a short period after the administration of estrogens to rabbits, he could observe vascular stasis and dilatation of the serosal surface of the uterus as seen through an abdominal window. He also stated, without presenting any details, that the intravenous administration of atropine prior to the estrogens prevented the hyperemia of this peracute reflex, and that therefore the action of estrogens was a parasympathetic reflex. Reynolds^{11, 12, 13} later studied the effect of estrogen administration on the acetylcholine content of the uterus of the castrate rabbit and demonstrated a sharp rise during the period of Pompen's peracute reflex. Emmens and his co-workers⁴ were unable to confirm Reynolds' results, but the nature of the method of determination of acetylcholine used by both observers is such that negative results are not necessarily significant. It may therefore be accepted that administration of estrogens causes a hyperemia and a rise in the acetylcholine content of the rabbit uterus. Soskin and his co-workers have apparently made the assumption that this applies in full to the endometrium and, indeed, to the endometrium of primates.

It has recently been shown,⁸ however, that the hyperemic effect of estrogens on the endometrium of the rabbit, as observed in transplants of endometrium to the anterior chamber of the eye, cannot be prevented by atropine, regardless of time and dose relationships. Furthermore, stilbestrol, which in Reynolds' experiments, was not responsible for a rise in acetylcholine content of the uterus, nevertheless produces a definite hyperemia of the endometrium. Two conclusions stem from these observations. One is that estrogenic effect on endometrium of the rabbit is not cholinergic in nature. The other, which follows by exclusion, is that the increase in acetylcholine content noted in the rabbit uterus after estrogen administration is due to increase in the myometrium.

The other facet of the hypothesis of Soskin and his co-workers is the relationship of vasodilatation to menstruation in primates. The very extensive researches of Bartelmez,¹ Daron,³ Markee,⁹ and others have shown that menstruation is preceded, not by hyperemia, but by a period of ischemia and regression. Markee has shown that regression is under way for a considerable length of time before bleeding begins, and that bleeding is the last in the series of events by which the endometrium returns to a resting state. Hence the "vascular failure" that Soskin and his co-workers proposed to correct by administration of cholinergic substances can hardly be responsible for amenorrhea if the endometrium has previously undergone follicular or progestational development.

Prostigmin effects are transitory when the drug is given hypodermically. They are manifest in five to ten minutes and last for no longer than three hours. It is difficult to envisage the mode of action of prostigmin in inducing menstruation under these circumstances, especially when it is administered every

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progesterone withdrawal bleeding, the studies were extended to include experiments in which the ability of large doses of estrogens to prevent progesterone withdrawal bleeding was employed to produce a simulation of amenorrhea. It is conceivable that some potent source of estrogens in the human being may produce amenorrhea in women following corpus luteum regression in just this manner. However, prostigmin has no effect on animals treated in this manner, down to postprogesterone doses of 1,250 International Units of Amniotin daily.

In conclusion, it may be stated briefly that, in the rhesus monkey, prostigmin has failed to induce menstrual bleeding in spontaneously occurring amenorrhea and has failed to alter the time of onset or duration of bleeding following varying courses of hormone administration and withdrawal. Inasmuch as there is reason to believe that the drug has some effect in the human being, there is a definite need for a critical clinical study in human amenorrhea.

Summary

1. The experimental studies of endometrial response to estrogens do not support the cholinergic concept of their mode of action. Menstruation in primates is not dependent upon hyperemia. The supposed theoretical basis for the use of prostigmin in human amenorrhea therefore cannot be accepted.

2. Administration of prostigmin hypodermically to rhesus monkeys does not induce menstrual bleeding in spontaneously amenorrheic animals, nor does it induce bleeding during estrogen administration, nor does it alter hormone-withdrawal bleeding following courses of estrogens, estrogens-progesterone or estrogens-progesterone-estrogens.

3. The efficacy of prostigmin as an emmenagogue and as a presumptive test for pregnancy is without experimental or critical clinical verification.

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TABLE I

| DRUG | AVERAGE HUMAN DOSE GRAINS | DOSE/KG. 60 KG. HUMAN MG./KG. | DOSE FOR DOGS MG./KG. | RATIO DOSES DOG/HUMAN | EFFECT ON DOGS |
|-----------------------------------|------------------------------|--|-----------------------------|--------------------------|---|
| Amytal and Seconal | Vi | 360 | 12.0 | 2:1 | Usually ataxic. Slight quieting first two hours, then hyperexcitable. |
| Scopolamine—1st dose | iii | 180 | 6.0 | SC/oral | |
| 45 min.—2nd dose | 1/150 | 0.4 | 0.025 | | |
| 1 hr. 45 min.—3rd dose | 1/200 | 0.3 | 0.02 | 4:1 | Dogs quieted but neither sleepy nor ataxic. |
| 3 hr. 15 min.—4th dose | 1/400 | 0.15 | 0.01 | | |
| 4 hr. 45 min.—5th dose | 1/400 | 0.15 | 0.01 | | |
| Pentobarbital | V | 300 | 13.4 | 3:1 | As with Amytal + Seconal. Ataxia marked. |
| Morphine | 1/6 | 10 | 0.67 | SC/oral | Emesis and defecation postinjection. Subdued |
| Meperidine ¹ (Demerol) | jss | 100 | 6.7 | 4:1 | 3 to 4 hours. No ataxia. |
| AN 148 ² (Methadon) | 1/12 | 5 | 0.34 | 4:1 | Quieted very slightly. No ataxia. |
| | | | | | Profuse salivation, 1 dog. Defecation post- injection. |
| | | | 0.67 | 8:1 | Salivation and defecation—all dogs postinjection. Slight ataxia. Very subdued. |

¹Meperidine (Demerol) was furnished through the courtesy of W. A. Curran of Winthrop Chemical Company.²Methadon, 6-dimethyl-4-, 4-diphenyl-3-heptanone hydrochloride (AN 148), was furnished through the courtesy of Dr. L. E. Josslyn of Abbott Research Laboratories.

THE ROLE OF DELAYED GASTRIC EMPTYING TIME IN THE ETIOLOGY OF ASPIRATION PNEUMONIA

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IN THE study of the problem of postdelivery atelectasis and aspiration pneumonia following general anesthesia, it was noted that the incidence of vomiting during anesthesia was inordinately high in obstetric patients. However, there were many patients in whom a diagnosis of aspiration pneumonia was made and in whom there was no recorded incidence of vomiting during or following delivery. In other patients who had undergone prolonged labor, undigested food and unexpectedly large quantities of fluid material sometimes appeared in the vomitus. It was not unusual for undigested food to be returned eighteen to twenty hours after the last ingestion of food. It was also noted that patients with such residual food and fluid after long labor often had abdominal distention in addition to that caused by the gravid uterus. It is well known that digestion may cease when labor starts.¹ However, the impression was gained from experience with deliveries in homes, where little "analgesie" medication is used, that anesthesia was better tolerated by such patients and the incidence of vomiting was much less.

It seemed worth while, therefore, to investigate in a comparative fashion the role which the medicaments employed in various "analgesie" and amnesic regimes of obstetric practice might play in delaying gastric emptying time.

Method

Mongrel dogs of either sex were selected and trained by handling until they were able to lie quietly while restrained on an x-ray table. They were maintained on a stock diet of horse meat, milk, corn meal, and dog food pellets in such fashion that regular weight gains were almost universal. After a fast of eighteen hours, a meal of approximately forty Gm. of barium sulfate in 150 c.c. of water was passed through a stomach tube. Emptying time of the stomach was determined to the nearest half hour by serial x-ray plates. A tablet of caseara (0.3 Gm.) was given by mouth to each dog after the stomach had emptied to prevent accumulation of barium sulfate in the lower gastrointestinal tract. An interval of one week was allowed between each successive experiment on the dogs.

Control determinations of gastric emptying time were made twice initially and after every two or three studies of the effects of medications. Drugs were given subcutaneously one-half hour before intubation. The doses and combinations of drugs employed were designed to simulate those used for "analgesia" in obstetrical practice and are indicated in Table I. A ratio of 4:1 between the average human dose in mg./kg. and the canine dose per kg. was used to

Methadon was doubled, the delay was quite pronounced in the 5 less sensitive dogs. Scopolamine in five divided doses, administered over a period of about 5 hours to 5 dogs, caused a definite and prolonged delay in 4. The tendency of scopolamine to prolong gastric emptying time was also demonstrable when added, according to the same divided dose regime, to average doses of morphine, meperidine, or pentobarbital. This effect was not as apparent with morphine, which in itself caused marked delay in evacuation of the stomach, but was more evident when combined with meperidine and most obvious with pentobarbital. When only two doses of scopolamine were used after pentobarbital, a delaying effect was observable in 2 of 3 dogs.

TABLE II. GASTRIC EMPTYING TIME IN HOURS FOLLOWING ANALGESIC MEDICATION

| DRUG | DOG NO. | 7 | 11 | 5 | A3 | 25 | A1 | 26 | 12 | 10 | 6 | AVG. |
|--|---------|-------|-------|-----|------|------|-----|------|-----|-----|------|-------|
| Control | | 2.0 | 5.0 | | 2.0 | 3.0 | 3.0 | 4.0 | 3.0 | 2.0 | 5.0 | |
| | | 2.0 | 2.0 | 3.0 | 6.0 | 2.5 | 2.5 | 5.0 | 5.0 | 3.0 | 4.5 | |
| | | 1.0 | 2.0 | 3.0 | 1.5 | 3.0 | 3.0 | 1.5 | | | | |
| | | 3.0 | 5.0 | 1.5 | 2.0 | | | 5.0 | | | | |
| | | 4.0 | 2.0 | | | | | | | | | |
| | | 5.0 | 2.5 | | | | | | | | | |
| AVERAGE | | 2.8 | 3.0 | 2.5 | 2.9 | 2.7 | 2.7 | 3.9 | 4.0 | 2.5 | 4.75 | 3.2 |
| Amytal and Seconal | | 3.0 | 2.75 | 2.0 | 5.5 | 4.0 | | 5.0 | | | 4.0 | |
| | | 6.0 | 3.0 | 3.5 | | | | | | | | 3.8 |
| Morphine | | 14.0 | 8.0 | | 10.5 | 6.0 | 6.0 | 5.0 | | | | 8.3 |
| Scopolamine × 5 | | 5.0 | 8.0 | 5.5 | | 9.0 | | 10.0 | | | | |
| | | | 10.0 | | | | | | | | | 7.7 |
| Morphine + Scop. × 5 | | 13.5+ | 13.5+ | 7.5 | | | | | 7.0 | 9.5 | | |
| | | 13.0+ | | | | | | | | | | 10.1 |
| Meperidine (Demerol) | | 4.0 | 6.0 | 3.0 | 6.5 | 6.5 | | 3.5 | | | | |
| | | 6.5 | 4.5 | | | | | | | | | 5.0 |
| Meperidine and Scop. × 5 | | 13.5 | 9.0 | | 12.0 | | 6.0 | 8.0 | | | | |
| | | | 9.0 | | | | | | | | | 9.7 |
| Pentobarbital (Nembutal) | | 2.5 | 2.0 | 9.0 | 2.0 | 3.0 | 2.0 | 3.0 | | | | 2.6 |
| | | | 4.0 | | | | | | | | | (3.5) |
| Pentobarbital + Scop. × 2 | | 9.5 | 6.0 | 3.0 | | | | | | | | |
| | | | | | | | | | | | | |
| Pentobarbital + Scop. × 5 | | | 7.0 | | 8.0 | 5.5 | 7.0 | 7.0 | | | | 6.9 |
| | | | | | | | | | | | | |
| AN 148 (Metha- don) 0.34 mg./kg. | | | | | | | | | | | | |
| | | 12.5 | 5.0 | | 6.0 | 4.0 | 3.5 | 3.0 | | | | 5.5 |
| | | 8.0 | 8.0 | | | | | | | | | |
| AN 148 0.68 mg./kg. | | 13.0 | | | 3.0 | | | | | | | |
| | | | 8.0 | | 6.0 | 10.0 | 8.0 | 9.0 | | | | 8.2 |

× = Number of doses.

One dog (No. 7) was very sensitive to the effects of morphine (emptying time 14 hours), morphine and scopolamine (13.0+ and 13.5+ hours) and Methadon (12.5, 8.0, and 13.0 hours). This animal showed the most severe depression and marked salivary and defecatory responses to the average dose of Methadon. A very active young dog (No. 11) that was studied 23 times in 9 months showed a very marked reaction to morphine and scopolamine. Another dog (No. 5)

allow for the relative species difference in surface area. This procedure is based upon the principle that the metabolism of hypnotic drugs is related to the general metabolic rate of the subject and therefore to surface area and to species differences in surface area. In the instance of the barbiturates, an additional factor of 50 to 100 per cent less than the calculated oral dose was allowed because of the necessity of using a parenteral route instead of the customary oral route of administration. The final ratio for Amytal and Seconal was 2:1 and for pentobarbital was 3:1.

The studies with Methadon (6-dimethyl-4, 4-diphenyl-3-heptanone hydrochloride), also known by the designation AN 148,² were included because of the present interest in this drug as a prospective analgesic agent of clinical value.

Results

The characteristic appearances of the dogs following medication are summarized in Table I. The barbiturates had a slight quieting effect but the animals were uniformly ataxic as indicated by slipping, weaving, and bumping objects when led into the x-ray room. Within two to three hours after injection, the quiescence had given way to hyperexcitability, although some ataxia remained for a longer time. This reaction has been described by Quigley et al.³ following the intravenous injection of pentobarbital. Morphine in the dosage used produced its initial symptoms, characteristic gastrointestinal effects of emesis and defecation from ten to fifteen minutes after injection. It was for this reason that intubation and deposition of the barium meal into the stomach were delayed until one-half hour after administration of all initial medications. The dose of scopolamine used was insufficient to prevent the initial gastrointestinal response to morphine. Scopolamine quieted the dogs but produced neither sleep nor ataxia. Meperidine (Demerol) produced a similar result.

Methadon has been stated to be a more potent analgesic than morphine.² In a dose of 0.34 mg./kg., Methadon quieted the dogs, but not as much as morphine in twice that dose. Salivation occurred in one dog and defecation in all. When the dose of Methadon was doubled, the attitude of the dogs resembled that produced by morphine and salivation and defecation occurred routinely shortly after injection. Ataxia was minimal in this group.

The normal range of gastric emptying time was from one to five hours; the average of 35 such control studies in the ten dogs, 3.2 hours. The averages for the particular dogs used in the study of each drug ranged from 2.9 to 3.2 hours. Normal gastric emptying times for this study were more rapid than the four and one-half to five and one-half hour averages found by Meek and Herrin⁴ when they allowed dogs to drink or eat a meal containing barium sulfate and milk. The speed with which the stomach was filled initially may have accounted for the early stimulus to motility in our studies. In considering the effects of medication, the control performances of each dog were used as the base line for estimating the effects in that animal. Average figures for each study are also given in Table II.

Amytal and Seconal in combination (7 dogs) delayed the emptying of the stomach scarcely at all. Most determinations were within the upper limits of normal for each animal. Similarly, there was no delay following pentobarbital (7 dogs) with but one exception which will be discussed later. Meperidine (Demerol) caused a slight delay, or an emptying time within the upper limits of normal for 4 of 6 dogs. The other two were well within normal ranges. Morphine (6 dogs) produced a very definite delay in all except one. Methadon (AN 148), in an average dose, caused a marked delay in one sensitive animal but only slight slowing in 3 of the remaining 5 animals. When the dose of

evident until the anesthetic is discontinued and the patient begins to recover her reflexes. Upon recovery of consciousness the patient may complain of pain in the chest and often may cough up sputum which is blood tinged. The color of mucous membranes and nail beds may be cyanotic; the temperature, pulse, and respiratory rate may be increased.⁸ Signs of respiratory difficulty, upon recovery of reflexes, may be out of proportion to any evidences of aspiration during the anesthetic procedure. Mendelson⁹ has shown that the acidity of aspirated gastric juice is an important factor in the pulmonary reaction leading to aspiration pneumonia.

Several preventive measures may be suggested. It should be re-emphasized from this discussion how important it can be that the physician impress upon his patient the dangers and uselessness of eating after labor starts, especially if the use of sedative drugs is anticipated. Emesis may be induced in patients admitted to the delivery floor with a history of recent ingestion of food. The advisability of passing a Levin tube and decompressing the stomach should be considered in those patients whose abdomens become tense and tympanitic during labor and while under analgesic medication. This has been practiced on occasion with relief of discomfort for the patient, improved effectiveness of medication, and more rapid progress of labor. Restraint and care in moving anesthetized patients and careful application of pressure, if pressure is to be used upon the fundus of the uterus, must be practiced. Probably one of the soundest procedures in the management of the patient with accumulated gastric content, as well as the patient with an upper respiratory infection, is the avoidance of general anesthesia entirely, by the use of caudal or low spinal anesthesia for delivery. The patient with spinal anesthesia retains reflex protection against regurgitation.

Conclusions

1. Studies of gastric emptying time in dogs under treatment with analgesic or amnesic agents or combinations of agents commonly used in obstetrics were made employing an x-ray technique.

2. The barbiturates, Amytal and Seconal or pentobarbital (Nembutal) seemed scarcely to delay gastric emptying time at all despite the production of marked ataxia.

3. Meperidine (Demerol) and Methadon (AN 148) in average doses delayed the time slightly except in particularly sensitive animals.

4. Morphine, and Methadon in large dosage, produced a definite and marked delay in the passage of the test meal.

5. Scopolamine in five doses over five hours definitely prolonged the emptying time and when added to other medications added to their effects.

6. The relationship of the effects of medication to the incidence of vomiting and regurgitation under general anesthesia and to aspiration pneumonia is discussed.

The author wishes to acknowledge the technical assistance of Miss Peggy Howard and Miss Elizabeth Glassco in carrying out this study.

had a characteristically rapid emptying time normally. The two seemingly paradoxical findings of emptying times of nine hours with pentobarbital and three hours with pentobarbital plus scopolamine for dog No. 5 perhaps can be related to the fact that it developed a pharyngeal abscess and died one week after the test with pentobarbital-scopolamine. However, no weight loss was observed until immediately before death.

Discussion

We have shown that in dogs certain analgesic or amnesic agents and combinations of such agents, in proportions commonly employed in obstetrics, may delay the passage of food from the stomach for a significant period of time. Such extension of time may vary from one to nine hours beyond the normal. Similar findings have been described previously for the individual drugs,^{2, 3, 5, 6, 7} but the comparisons made here are somewhat different from those previously made.

The data presented may serve to re-emphasize the particular relationship which the smooth-muscle action of "analgesic" drugs has to the production and conduct of anesthesia for obstetric patients. Delay in emptying the stomach of food may be brought about by the emotional and physical strain of labor,¹ in synergism with the smooth-muscle actions of these drugs. We have reason to believe that delays comparable with those recorded in these experiments may occur in human beings. A total emptying time of from eight to fourteen hours would in many instances extend, if labor started shortly after eating, into the second stage of labor. Undigested food would remain in the stomach of this patient at the time when normally she would be induced into anesthesia for delivery. Oftentimes such residual food is augmented in volume by accumulated fluid and gas. Thus, within the already crowded abdominal cavity, the stomach and distended loops of bowel may occupy an inordinate amount of space.

Anesthetic management of such a patient with gastrointestinal distention may be complicated in one or both of two ways: (1) the attainment of an adequate concentration of anesthetic in the blood stream and brain may be difficult and slow because respiratory exchange may be diminished in the supine position by the pressure of the abdominal contents against the diaphragm and slow passage through the second anesthetic stage of heightened reflexes may lead to vomiting or to excessive accumulation of mucus; (2) regurgitation of small amounts of gastric fluid and undigested food may occur as from a bulb syringe, when the uterus is caused to compress the stomach. This is especially so if the patient is moved under anesthesia in such manner that the pelvis and abdomen are flexed upon the thorax. It is also true if pressure, exerted upon the fundus of the uterus to aid in the expulsion of the fetus, inadvertently is directed dorsally upon the distended stomach, instead of in the axis of the uterus. The premedicated, anesthetized patient is unprepared reflexly to guard against such regurgitation and the anesthetist is not warned by the usual reflex signs of vomiting that regurgitation has taken place. Aspiration into the trachea of regurgitated gastric contents might therefore occur in this crucial interval and the incipient effects of irritation by the acid material might not be very

AGE, INCIDENCE, AND DISTRIBUTION OF 4,652 CASES OF CARCINOMA OF THE CERVIX

With a Report of Three Cases During the First Two Decades of Life

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ONE of the important factors in the approach to the cancer problem is early diagnosis, which is largely in the hands of the family physician. It is imperative that he be familiar with the incidence of cancer in relation to the age of the patient.

An age study was therefore made of 4,652 patients with cases of carcinoma of the cervix admitted to the Roswell Park Memorial Institute during the years 1914 to 1946, inclusive. These cases comprise 15 per cent of all admissions to the hospital and 62 per cent of all malignant gynecologic admissions. During this period there were approximately 1,500 patients with carcinoma of the body of the uterus admitted to the hospital, about one-third of the number of cases of carcinoma of the cervix. Comparing the occurrence of carcinoma of the cervix with that of carcinoma of the body of the uterus, the ratio is 3 : 1.

The data of 4,652 cases of carcinoma of the cervix have been tabulated according to age distribution, as shown in Table I. The same data are shown graphically in Fig. 1, Curve A. This curve represents only the age at the time of admission of patients having carcinoma of the cervix; it shows a definite peak at the age of 47 years, but it must not be interpreted to mean that the peak of incidence of the female population as a whole is at the age of 47 years. In order to obtain the age incidence in a more representative manner, the data of Table I have been computed for the different age groups in relation to the female population of the State of New York (1940 census). These calculations are shown graphically in Fig. 1, Curve B.

The 4,652 patients with carcinoma of the cervix represent women from New York State admitted to the Roswell Park Institute during the years 1914 to 1946 inclusive, and do not represent all the cases of this type in the entire state. Nevertheless the number is a large one, and therefore it is considered to be fairly representative. From these data it can be concluded that carcinoma of the cervix does occur in any age period subsequent to the first decade and attains a maximum of incidence at the age of 57 years. It may be gathered that carcinoma of the cervix under the age of 20 years is exceedingly rare, but it does occur in an appreciable percentage of cases between the ages of 20 and 30 years as is shown in Table I, where 146 cases or 3 per cent occurred in this decade. Carcinoma of the cervix occurs three times as frequently after the age of 75 years as before the age of 25 years. Approximately 20 per cent of our cases occurred before the age of 40 years. About 60 per cent were found immediately preceding and including the average menopause age, between 40 and 60 years of age. It was still relatively

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2065 ADELBERT ROAD

TABLE II. AGE DISTRIBUTION IN CARCINOMA OF THE CERVIX, 4652 CASES
ACCORDING TO THE HISTOLOGIC CLASSIFICATION

| AGE | SQUAMOUS CARCINOMA | | ADENOCARCINOMA | | ADENOACANTHOMA | |
|-------------------|--------------------|----------|----------------|----------|----------------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| 15-19 | 2 | 0.045 | 0 | 0 | 0 | 0 |
| 20-24 | 25 | 0.57 | 0 | 0 | 0 | 0 |
| 25-29 | 117 | 2.7 | 2 | 1.2 | 2 | 1.6 |
| 30-34 | 283 | 6.5 | 4 | 2.4 | 8 | 6.6 |
| 35-39 | 450 | 10.5 | 12 | 7.4 | 6 | 4.9 |
| 40-44 | 586 | 13.4 | 16 | 9.9 | 9 | 7.4 |
| 45-49 | 717 | 16.4 | 24 | 14.8 | 18 | 14.9 |
| 50-54 | 700 | 16.0 | 29 | 17.9 | 15 | 12.4 |
| 55-59 | 574 | 13.1 | 22 | 13.6 | 23 | 19.0 |
| 60-64 | 437 | 10.0 | 20 | 12.3 | 20 | 16.5 |
| 65-69 | 256 | 5.8 | 18 | 11.1 | 12 | 9.9 |
| 70-74 | 141 | 3.2 | 8 | 4.9 | 7 | 5.8 |
| 75-79 | 63 | 1.4 | 4 | 2.4 | 1 | 0.82 |
| 80-84 | 20 | 0.45 | 1 | 0.62 | 0 | 0 |
| | 4369 | | 162 | | 121 | |
| PER CENT OF TOTAL | 94.0 | | 3.4 | | 2.6 | |

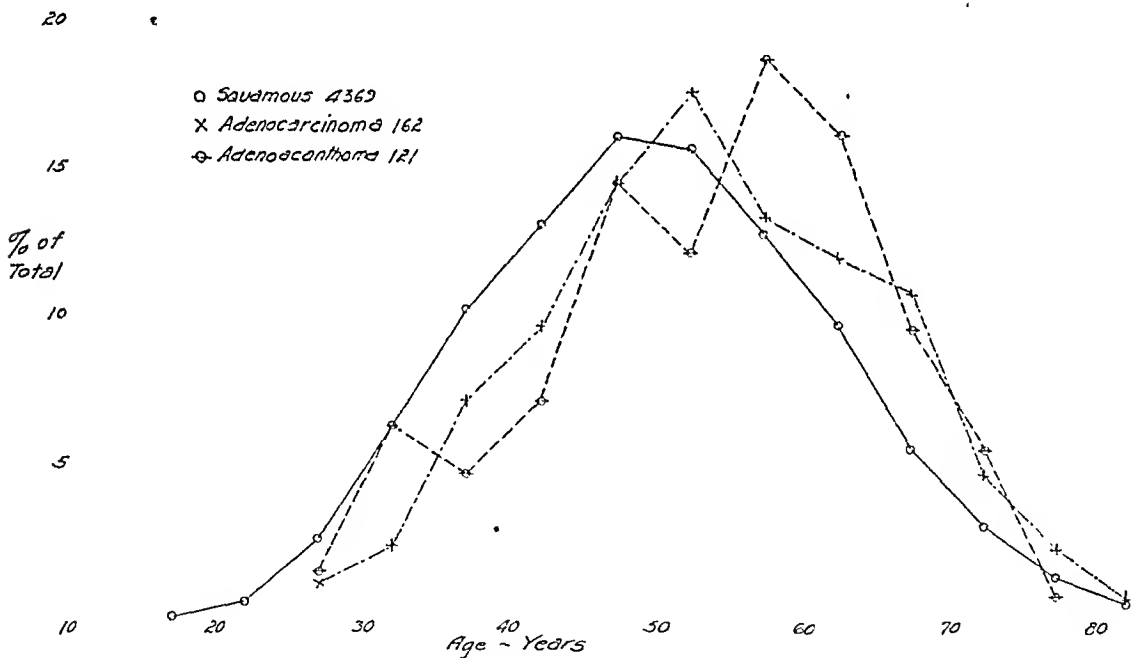


Fig. 2.—Showing the age distribution at the time of admission of the three histologic types of carcinoma of the cervix.

0—0, 4,369 cases of squamous cell carcinoma of the cervix.

X-----X, 162 cases of adenocarcinoma of the cervix.

0-----0, 121 cases of adenoacanthoma of the cervix.

at admission of the cases in these three groups is shown in Fig. 2. It is evident that the majority of the cases of squamous cell carcinoma occur approximately five years earlier than those of adenocarcinoma and adenoacanthoma, and reach a peak at admission at the age of 47 years. Adenocarcinoma occurs later in life, reaching a peak at admission at the age of 52 years, whereas adenoacanthoma shows two peaks, one at 47 years, and

TABLE I. DISTRIBUTION OF CASES OF CARCINOMA OF THE CERVIX
ACCORDING TO AGE AT ADMISSION

| AGE | NUMBER ADMITTED | PER CENT OF TOTAL ADMITTED | FEMALE POPULATION N. Y. STATE CENSUS 1940 | RATE PER 10,000* |
|-------|--------------------|-------------------------------|---|---------------------|
| 15-19 | 2 | 0.05 | | |
| 20-24 | 25 | 0.6 | 594,549 | 0.42 |
| 25-29 | 121 | 2.6 | 616,934 | 1.96 |
| 30-34 | 295 | 6.3 | 593,492 | 5.0 |
| 35-39 | 468 | 10.1 | 561,084 | 8.3 |
| 40-44 | 611 | 13.1 | 530,311 | 11.5 |
| 45-49 | 759 | 16.3 | 476,854 | 15.9 |
| 50-54 | 744 | 16.0 | 408,192 | 18.2 |
| 55-59 | 619 | 13.3 | 319,838 | 19.4 |
| 60-64 | 477 | 10.2 | 264,708 | 18.0 |
| 65-69 | 286 | 6.1 | 207,659 | 13.8 |
| 70-74 | 156 | 3.3 | 143,218 | 10.9 |
| 75-79 | 68 | 1.5 | 146,417 | 6.1 |
| 80-84 | 21 | 0.5 | | |
| | 4,652 | | | |

*Rate of number admitted, calculated from columns 2 and 4.

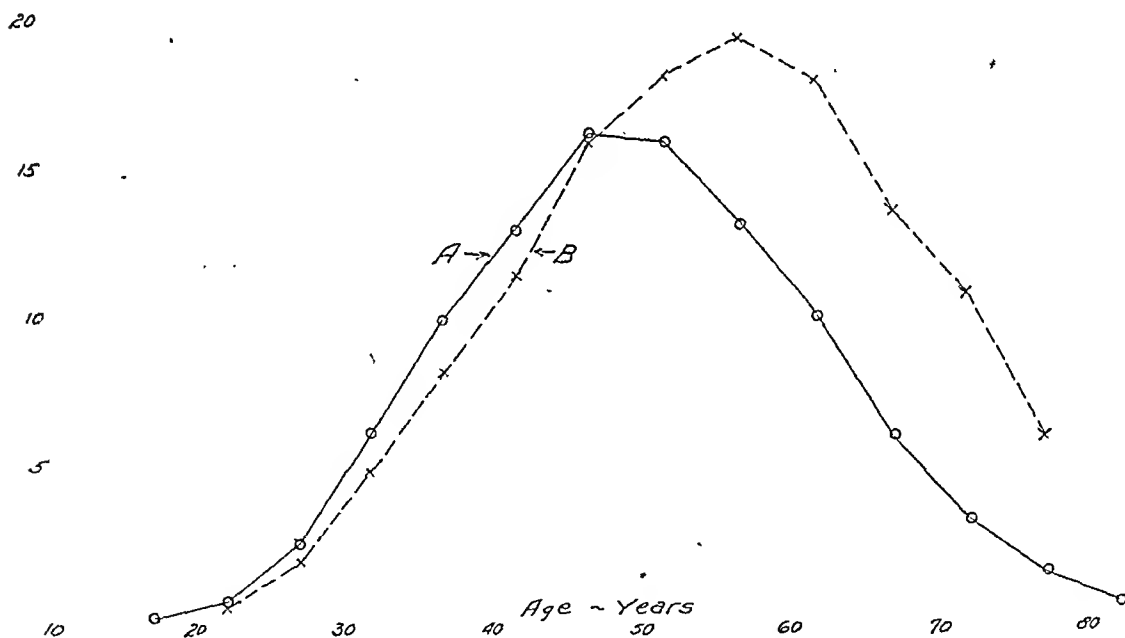


Fig. 1.—Showing the age distribution of 4,652 cases of carcinoma of the cervix.

O—O, age at admission, per cent of total.

X—X, age incidence per 10,000 of the normal female population of New York State, 1940 census.

common until the age of 65 years, after which there was a gradual decrease in the number. This decrease at first glance would lead one to suppose that it was due to the effect of the normal death rate after the age of 65 years. However, by referring to Table I, Columns 4 and 5, it is evident that while the female population is decreasing with increasing age, the rate of cancer incidence of the cervix is decreasing at a faster rate.

All the cases of carcinoma of the cervix were subdivided into their respective histologic classifications as shown in Table II. A plot of the ages

and posterior lips of the cervix and both broad ligament areas, as well as beginning infiltration of the rectum and base of the bladder. A biopsy showed a squamous cell carcinoma of the cervix, Grade III (see, Fig. 4). Clinically, she was a Stage IV. On Aug. 13, 1931, radon seeds were implanted into the cervix and radium tubes inserted into the uterine canal; total seeds and tubes were 5,140 milliecurie hours. There was marked regression of the tumor during the next few months. On March 19, 1932, the patient was re-admitted, complaining of discharge and bleeding. Pelvic examination revealed a hard, nodular cervix, with pelvic infiltration. The patient again received seeds and tubes for a total of 4,500 milliecurie hours, but improvement was negligible. The patient died of disease on Aug. 26, 1932. No autopsy was performed.

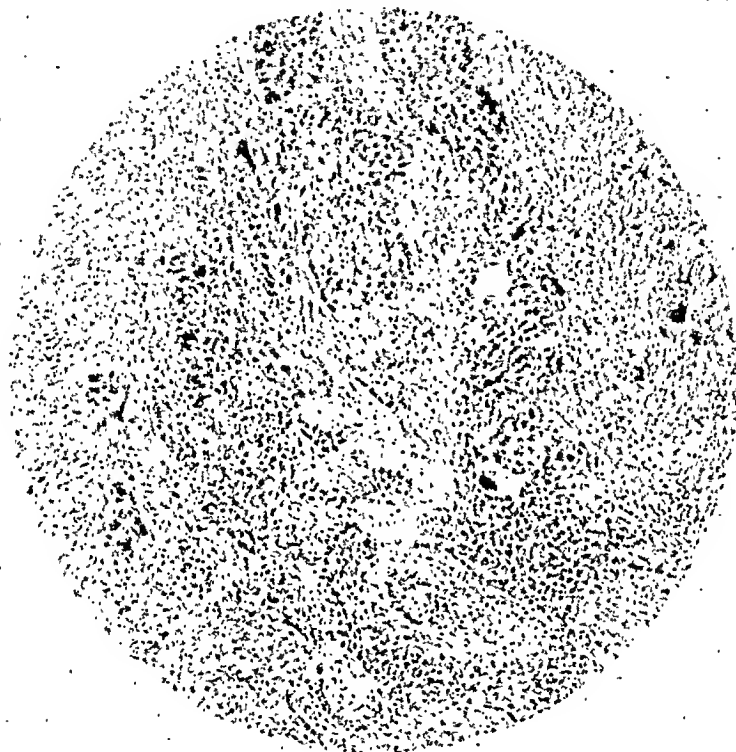


Fig. 3.—Case 1. Section of tissue from the cervix shows a squamous cell carcinoma. Some of the tumor cells are differentiated in character, but the majority are found to be anaplastic. This tumor was infiltrative in character. Diagnosis: Squamous cell carcinoma, Grade II plus.

CASE 3.—K. W., 20 years of age, gravida 0, married four years, was first seen at the clinic of the Roswell Park Institute on March 28, 1934. The patient stated that she had had a watery discharge for four years. Menstruation began at 13 years of age. The menses were always regular until the last period, at which time there was a heavy, steady flow persisting for one month previous to admission. Her family physician was consulted for the first time on March 21, 1934. She was referred here for treatment. Pelvic examination revealed a fungating epithelioma involving the whole cervix and extending onto the vaginal mucous membrane. It was classified as a clinical Stage II. A biopsy was reported to be a squamous cell carcinoma of the cervix Grade II (see Fig. 5). Treatment over a period of forty-eight hours consisted of radon seeds, radium tubes, and x-radiation, for a total of 8,338 r. The patient has been followed for the past thirteen years, and examination on March 13, 1947, revealed no evidence of disease.

The information contained in these reports is briefly summarized in Table III.

In reviewing the literature, we found that Pollack and Taylor² recently made a survey of all the reported cases of true carcinoma of the cervix which occurred during the first two decades of life. They composed a chart of thirty cases, and added one of their own, making

the other 57 years. These two peaks may be due to the fact that there are comparatively few cases of adenoacanthoma in this series of cases, and therefore these peaks may not be statistically significant. On the other hand, they could signify that adenoacanthoma falls into two separate groups, depending on the location of the primary focus from which it is histologically derived, namely, either the cervix or the fundus. The reason for this observation is that the one peak at 47 years of age coincides with the peak of the squamous cell carcinoma of the cervix curve, and the other peak at the age of 57 years is identical with that which we have found to be characteristic of the fundus carcinoma cases.

Novak¹ states, "that there has been considerable discussion as to whether adenoacanthoma arises from a double matrix, or whether the squamous transformation is a later development in an adenocarcinoma." The later theory is the one which seems to have the widest acceptance, but apparently the former viewpoint is brought out by the curve in Fig. 2, with its double peak.

The age of the youngest patient in the squamous cell carcinoma series is 18 years, and that of the oldest is 84 years. The age of the youngest patient of the adenocarcinoma and adenoacanthoma series is 25 years, and the oldest is 83 years for the former and 79 years for the latter. There is a total of three cases in the first two decades of life, which are of particular interest in regard to the age distribution of carcinoma of the cervix. These cases are reported in detail as follows:

Case Reports

CASE 1.—L. P., aged 20 years, American-born married woman, gravida 0, was first seen in the clinic at the Roswell Park Institute on July 27, 1914. The patient had consulted her family physician one month prior to admission. She had been complaining of a watery discharge and irregular vaginal bleeding for the past two years. She began to menstruate at the age of 12 years; the menses occurred regularly every twenty-eight days and lasted for three or four days with moderate flow. There was no associated discharge or pain, and the menses appeared normal in all respects. At the age of 18 years she began to have intermenstrual bleeding and mild bloody discharge. She also had a sudden and profuse vaginal hemorrhage before entering the clinic. Pelvic examination revealed a fundus which was normal in size, the right adnexa were normal, the left adnexa showed a large, tender mass. The cervix was replaced by a large ulcerating cauliflower-type tumor mass. There was fixation in both broad ligaments. Biopsy of the tumor proved to be a squamous cell carcinoma of the cervix, Grade II (see Fig. 3).

This patient received a series of eight treatments of low voltage x-ray, using multiple ports to the pelvis and perineum, with no notable improvement. The patient died three months after admission, and an autopsy revealed multiple metastases to the lungs, liver, omentum, and pelvis. In retrospect, this case would be classified according to the League of Nations as a clinical Stage IV.

CASE 2.—G. A., 18 years of age, gravida iii, married five years, was first seen at the Clinic of the Roswell Park Institute on Aug. 11, 1931. The patient stated that she had been flowing excessively at frequent intervals for the past seven months. Her family physician saw her for the first time one month prior to admission to the clinic. No previous treatment had been given. Her periods began at 12 years of age and were regular, every four weeks with moderate flow, lasting five to six days. Her present bleeding she attributed to her last pregnancy which was seven months prior to admission. Pelvic examination showed an ulcerating, indurated tumor with involvement of the anterior

a total of thirty-one. With those added in this report, the total has been increased to thirty-four. Of these thirty-four cases, twenty-two, or 65.7 per cent, were patients with adenocarcinomas; seven, or 20.6 per cent, were patients with squamous cell, and four, or 11.8 per cent, were not classified. The pathology of one patient showed both squamous and glandular features, and probably fell into the adenocarcinoma group. The relation between squamous cell carcinoma and adenocarcinoma of the cervix in this younger group is the reverse of that found in the group as a whole.

TABLE III. SUMMARY OF CASES 1, 2, AND 3.

| CASE | HISTOLOGY | AGE (YEAR) | REMARKS | FIVE-YEAR SURVIVAL |
|------|--------------------|---------------|--|-----------------------|
| 1 | Squamous carcinoma | 20 | Died of disease, 3 months, with multiple metastases. Treatment x-ray therapy | No |
| 2 | Squamous carcinoma | 18 | Died of disease, 1 year. Treatment radium therapy | No |
| 3 | Squamous carcinoma | 20 | Alive and well 13 years. Treatment radium and x-ray therapy | Yes |

Of the thirty-four cases, there were five cases which survived five years. This represents approximately 15 per cent five-year survivals free of disease. While this survival is smaller than that for the entire group of 4,652 cases, yet, because of the poorer expectancy in the early age groups, this represents a fairly encouraging survival rate for the early age group.

Summary

The results of a study of the age distribution of 4,652 cases of carcinoma of the cervix have been presented, showing both the ages of incidence and the ages at admission, together with a breakdown into the age distribution of the three histologic groups.

A detailed report is given of three cases of squamous cell carcinoma of the cervix occurring in the second decade of life.

It is important that the family physician realize that malignancy of the cervix may occur at any age period after the first decade of life, and the possibility of the presence of carcinoma of the cervix should not be eliminated solely because of the age of the patient.

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2. Pollack, R. S., and Taylor, H. C., Jr.: AM. J. OBST. & GYNEC. 53: 135, 1947.

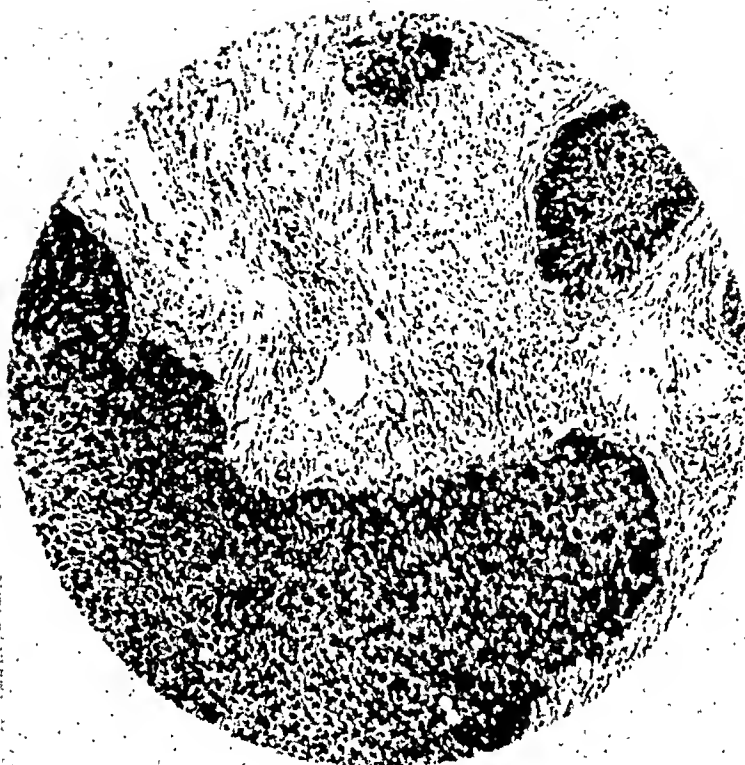


Fig. 4.—Case 2. Section of tissue from the cervix showing a squamous cell carcinoma. Tumor cells are anaplastic in character, and fail to show any degree of differentiation. Diagnosis: Squamous cell carcinoma of the cervix, Grade III.



Fig. 5.—Case 3.—Section of tissue from the cervix shows a squamous cell carcinoma. As a rule the tumor cells are well differentiated in character with extensive keratinization and pearl formation. Some inflammatory reaction is found in the supporting stroma. Diagnosis: Squamous cell carcinoma of the cervix, Grade II.

milligram capsule filtered by 2 millimeters of platinum is placed in the vagina anteroposteriorly across the cervix, and a 10 milligram capsule similarly filtered is placed in each end of a colpostat. This technique utilizes a total of 60 milligrams of radium which is left in place for a period of one hundred hours. Not infrequently this dosage is divided into two applications at an interval of one month. Because of the potent dangers of infection and of injury to the ureters and the uterine vessels we have abandoned the use of interstitial radium needles. The lower bowel is cleansed by an enema prior to the application and a catheter remains in the bladder. The Trendelenburg position is maintained throughout the period of radiation to protect the intestinal tract.

Results of Radiation Therapy

The absolute results of any form of treatment for cancer must be based upon the number of patients who are living and free from evidence of cancer after a standard number of years compared to the number of patients who apply for treatment. The relative survival rate is calculated upon the number of patients who were actually treated. Unfortunately there is such a wide variation in methods of reporting results that comparison of survival rates is extremely difficult.

The average absolute five-year survival rate following combined radiation therapy as estimated from present-day reports is in the neighborhood of 28 per cent. It is interesting and perhaps informative to note that this rate is in direct proportion to the recognized absence of involvement of regional lymph nodes. This poses the question of whether cancerous lymph nodes are susceptible to present methods of radiation therapy.

A fair average of five-year salvage figures for growths apparently limited to the cervix is 75 per cent; for those questionably limited is 50 per cent; for those which have invaded the broad ligaments is 20 per cent; and in the group of cases in which the growth has involved the entire pelvis, the five-year salvage is practically nil.

These results, reported by a large number of surgeons and radiologists, are quite comparable with the results obtained by such master surgeons as Bonney and Wertheim with the radical operation. The primary mortality is practically nil and urinary fistulas and other untoward postoperative sequelae are rare.

Report of Cases From Pennsylvania Hospital

The following portion of this presentation is based upon the patients with carcinoma of the cervix observed and treated in the Pennsylvania Hospital from 1933 through 1941. During the first half of this period approximately one-third of the patients were treated on the general surgical service; since 1937 all such cases have been admitted to the gynecologic service where the methods of management have been more uniform.

TABLE I. CARCINOMA OF THE CERVIX, PENNSYLVANIA HOSPITAL. 1933 TO 1941

| | NUMBER | PER CENT |
|-------------------|--------|----------|
| Patients seen | 130 | 100 |
| Patients treated | 122 | 94 |
| Patients followed | 125 | 96 |

As seen in Table I, only eight of the 130 patients were considered to have involvement too extensive to warrant treatment. All of these died within a few weeks of their admission. Ninety-six per cent of the patients have been

THE TREATMENT OF CARCINOMA OF THE CERVIX*

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(From the Division of Obstetrics and Gynecology, Pennsylvania Hospital)

KELLY and Burnham of Baltimore in 1912 initiated the elective treatment of carcinoma of the cervix with radium. The negligible primary mortality, the absence of postoperative morbidity, the almost miraculous immediate response and the high incidence of apparent cures resulted in its adoption as the treatment of choice in most of the major gynecologic clinics throughout the world.

The technique of radiation therapy has undergone a gradual evolution during the past thirty-five years; with increase of knowledge of the physics of radiation and the biologic reaction of tissues to this form of therapy it is rare indeed to see the needless destruction of tissue which was formerly referred to as "the usual radium slough." In most clinics at the present time treatment with high voltage x-ray precedes the local application of radium. This has the fourfold advantage of devitalizing the cancer cells before local manipulation may cause their dissemination, at least partial sealing of lymphatic channels, clearing up the ever present local infection, and an amazing restoration of the cancer-distorted anatomic relationships.

At Pennsylvania Hospital we have given 2,000 to 2,800 roentgens as measured in air to one 15 by 15 centimeter port anteriorly and posteriorly. For greater protection of the bladder and lower bowel a strip of lead four centimeters wide and five millimeters thick is placed on the skin in the midline prior to each treatment. The remaining areas are filtered by one millimeter of aluminum and 0.5 millimeter of copper. Two hundred kilovolts are utilized at a distance of 50 centimeters. The effective wave length is 0.160 Au, and the half value layer is 0.90 millimeters of copper. If well tolerated, 200 roentgens are administered anteriorly and posteriorly three times each week. In our earlier cases two lateral ports were used, but this was discontinued because of the high incidence of fracture of the neck of the femur following this relatively ineffectual amount of exposure. The addition of the lead strip, which reduces the depth dose to the midline structures by 50 per cent, has diminished the number of both early and late bladder and bowel reactions.

More recently the abdominal and loin ports have been supplemented by a cervical port, the radiation being delivered through an intravaginal cone. Behney, and more recently, Taylor and Twombly, have reported promising improvements in salvage following use of this method.

Six weeks after completion of the x-ray cycle the local application of radium is made. Techniques vary widely in minor details, but the consensus is to give approximately 6,000 milligram hours to the cervical area, including the cavity of the uterus and the bases of the broad ligaments. This dosage will vary upward if small amounts of heavily filtered sources of radiation are used, or downward if larger quantities of radium are utilized. Our own technique for the past ten years at the Pennsylvania Hospital is to place three 10 milligram capsules into the cervical canal filtered by 1 millimeter of platinum. One 10

*Presented, by invitation, before the Chicago Gynecological Society, May 16, 1947.

TABLE VI. HISTOLOGIC TYPE

| | NUMBER | PER CENT |
|----------------|--------|----------|
| Squamous cell | 112 | 86.1 |
| Adenocarcinoma | 18 | 13.9 |
| Total | 130 | 100.0 |

of malignancy, as we found some years ago that the high radiation sensitivity of the more malignant tumor and the relative radiation resistance of the more slowly growing cancer account for a practical equality of end-results in the two groups. It is our belief that all patients should be given the maximal amount of radiation therapy.

TABLE VII. ABSOLUTE FIVE-YEAR SALVAGE ACCORDING TO HISTOLOGY

| TYPE | NUMBER OF CASES | FIVE-YEAR SALVAGE | |
|----------------|-----------------|-------------------|----------|
| | | NUMBER | PER CENT |
| Squamous cell | 112 | 30 | 23.0 |
| Adenocarcinoma | 18 | 6 | 33.3 |
| Total | 130 | 36 | 27.6 |

The number of cases of adenocarcinoma is too small to be significant; the results are recorded for whatever value they may be in a larger collected series.

TABLE VIII. ABSOLUTE FIVE-YEAR SALVAGE ACCORDING TO EXTENT

| STAGE | NUMBER OF CASES | FIVE-YEAR SALVAGE | |
|-------|-----------------|-------------------|----------|
| | | NUMBER | PER CENT |
| I | 7 | 6 | 85.7 |
| II | 38 | 18 | 47.3 |
| III | 66 | 12 | 18.2 |
| IV | 19 | 0 | 0. |
| Total | 130 | 36 | 27.6 |

Our results as shown in Table VIII confirm the accepted fact that the extent of the disease is the only valuable indicator in prognosis. Four-fifths of the Stage I cases became five-year survivors, while none of the Stage IV patients lived more than a few months.

TABLE IX. ABSOLUTE FIVE-YEAR SALVAGE ACCORDING TO "OPERABILITY"

| STAGE | NUMBER OF CASES | FIVE-YEAR SALVAGE | |
|------------|-----------------|-------------------|----------|
| | | NUMBER | PER CENT |
| I and II | 45 | 24 | 53.3 |
| III and IV | 85 | 12 | 14.1 |
| Total | 130 | 36 | 27.6 |

These figures (Table IX) are re-arranged from the preceding table so that comparison can be easily made with survival results following radical surgical therapy. The five-year salvage of 53.3 per cent compares favorably with Wertheim's 42.9 per cent, and with Bonney's 53 per cent survival rate in 300 cases in which there was no lymph node involvement.

In Table X an attempt is made to correlate the five-year survival rate with the amount of radiation therapy. "Adequate" therapy indicates 6,000 milligram hours of radium and 2,000 roentgens of x-ray to each of four pelvic ports. "Borderline" therapy includes those patients who received from 3,600 to 6,000

followed, despite the fact that the war years caused a considerable disruption of our cancer clinic. The five patients who were lost were counted as having died of cancer.

TABLE II. EXTENT OF DISEASE (SCHMITZ)

| STAGE | NUMBER | PER CENT |
|-------|--------|----------|
| I | 7 | 5.4 |
| II | 38 | 29.2 |
| III | 66 | 50.8 |
| IV | 19 | 14.6 |
| Total | 130 | 100.0 |

Table II indicates that our material was composed of the usual preponderance of late cases; in two-thirds of the cases the growth had extended beyond the confines of the uterus. It is hoped and rather reasonably expected that education of the public will result in reversal of these figures.

TABLE III. AIM OF TREATMENT

| | NUMBER | PER CENT |
|-----------------|--------|----------|
| Curative | 111 | 85.4 |
| Palliative only | 11 | 8.4 |
| No treatment | 8 | 6.2 |
| Totals | 130 | 100.0 |

The figures in Table III show that eleven patients were treated only for palliation. These were Stage IV cases in which a minimal amount of x-ray or radium therapy was utilized in the hope of temporary control of bleeding. The amount of treatment was so small in terms of curative therapy that they would be more correctly recorded as not having received any treatment. The remaining 111 cases constitute the group on which the relative survival figures are calculated.

TABLE IV. ABSOLUTE FIVE-YEAR SALVAGE

| | NUMBER | PER CENT |
|---------------------------------|--------|----------|
| Patients seen | 130 | 100 |
| Patients living 5 or more years | 36 | 27.6 |

The absolute five-year salvage rate is based upon the number of survivors free from evidence of cancer as compared to the total number seen during the period. The latter figure includes nineteen patients who were not given a "curative" amount of therapy.

TABLE V. RELATIVE FIVE-YEAR SALVAGE

| | NUMBER | PER CENT |
|---------------------------------|--------|----------|
| Patients treated (curative) | 111 | 100 |
| Patients living 5 or more years | 36 | 32.4 |

The relative five-year salvage is based upon the 111 patients who were given the full or near-full amount of treatment. Approximately one-third of these patients have survived from five to thirteen years with no present evidence of cancer.

The usual distribution of histologic types of growth is shown in Table VI. No attempt has been made to correlate the end-results with the histologic degree

Taylor, H. C., Jr., and Twombly, Gray: *Am. J. Roentgenology* 56: 513, 1946.
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807 SPRUCE STREET
 255 SOUTH 17TH STREET

Discussion

DR. HERBERT E. SCHMITZ.—At the dedication of the Tumor Clinic at Henrotin Hospital in 1939 one of the guest speakers was Dr. Joseph Vincent Meigs. During the course of his presentation he made the statement, "I believe the treatment of carcinoma of the cervix is surgical." Since that time there has been a tremendous trend mostly by those of little experience to follow in the footsteps of Meigs. I think before long he is going to realize that his end-results do not justify the heroic measures that he is undertaking with his surgical attack. It is going to take ten or fifteen years before those who have followed in his footsteps will become cognizant of that fact and finally give up radical operation. When I received Dr. Kimbrough's paper and read it some weeks ago, I thought it would be of interest to take a comparable number of years in our clinic and break down those cases to try and support what he had to say.

The one difference is this, that beginning in 1933 we instituted higher voltage x-ray in the treatment of cervical carcinoma, x-ray in the range of 800,000 volts. The radium dose that we had previously used and which had been reported in previous publications since 1914 has remained the same. Our method of radium application is to give in divided doses 4,500 milligram hours of radium placed in the cervical canal, filtered with 2 mm. of brass and 3 mm. of para rubber. The length of the capsule is altered to fit conditions predominant in the canal of the cervix.

I wish to momentarily digress from that to call your attention to a recent paper by Rusty Purtell of Seattle in which he makes the statement that the treatment of carcinoma of the cervix should be in the hands of the radiologist, and that the results will never be satisfactory if the gynecologist is going to carry on radium treatment, and the radiologist roentgen ray therapy. He says it takes the knowledge of the radiologist in physics of radiation to know how to apply radium because of the changes in the cervical canal. It is my opinion that the gynecologist is more competent to dilate the cervical canal and apply radium than the radiologist. I think we should rise in defense of our position there.

During a comparable period, 1933 to 1942, there were 422 cases of carcinoma of the cervix in the Institute. I have broken this down into recurrent and primary cases, because with the advent of higher voltage many patients were sent in to the Institute who had previously been radiated in the hope that the higher voltage would be of benefit. We know very definitely that previous radiation alters the sensitivity of the cancer cells to radiation, not only because of the effect on the cell itself, but because of a change in the environment in which that cell finds itself; in other words, the sensitivity of the tumor cell in the cervix is altered when it goes into the vagina or vaginal mucosa. Therefore, we must delete these recurrent cases. That leaves us with 166 cases during that time that had no previous radiation. Dividing those into the four groups of Schmitz we have:

| | |
|-----------|----------|
| Group I | 11 cases |
| Group II | 37 cases |
| Group III | 70 cases |
| Group IV | 48 cases |

It is interesting to note the slight variation in Groups I and II, Dr. Kimbrough having seven in Group I and thirty-eight in Group II. In Group III the radiation as carried out is 800 kilovolts x-ray with a filtration of 1 mm. of lead, 1½ mm. of tin, 2 mm. copper, and 3 mm. aluminum. Our aim is to give 4,000 r into the midpelvis and into the tumor-bearing area. If we can do that with two fields we do not resort to three or four. We have been told if you use a large field of x-ray at the outer limits of your field you lose so many roentgens. With 10 cm. depth dose we lose four to ten roentgens at the outer edge; with

milligram hours of radium and at least 1,600 roentgens of x-ray to each of four pelvic ports. The "uneoordinated" received less therapy than the "Borderline." While the number of cases is too small to warrant definite conclusions, there is an indication that our present plan of treatment offers a better chance of five-year survival than lesser amounts of therapy.

TABLE X. RELATIVE FIVE-YEAR SALVAGE ACCORDING TO ADEQUACY OF TREATMENT
(STAGES I, II, AND III)

| TREATMENT | CASES | | FIVE-YEAR SALVAGE | |
|---------------|--------|----------|-------------------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT |
| Adequate | 36 | 33 | 14 | 38.8 |
| Borderline | 28 | 25 | 8 | 25.8 |
| Uncoordinated | 47 | 42 | 14 | 29.8 |
| Total | 111 | | 36 | 32.4 |

Revival of the Radical Surgical Approach

Within the past few years Meigs of Boston, Taylor of New York, Counsellor of the Mayo Clinic, Morton of San Francisco, Carter of Durham, and a few others have advocated a return to the radical Wertheim operation combined with Taussig's lymphadenectomy for the treatment of certain early selected cases. Meigs has recently detailed his reasons for this decision as follows:

- "1. If the cervix is removed, there is no chance for recurrence in it.
- "2. If the cervix is removed no cancer can grow in it as a recurrence.
- "3. Certain cancers of the cervix are radiation-resistant.
- "4. From the work of Bonney and Taussig it has been proved that about 20 per cent of patients with lymph-gland involvement can be salvaged by surgery."

Those who advocate this method restrict its use to good operative risks in whom the growth involves not more than the entire cervix and the upper portion of the vagina. It is not applicable to those in whom the parametrium is invaded.

It is a credit not only to Meigs' consummate skill, but also to the numerous advances in modern surgery that he was able to perform this exacting procedure ninety-one times without an operative death, and that he has had forty consecutive cases without development of a single urinary fistula. Of the 36 patients who had been operated upon more than three years previously, he reported in 1946 that 77.7 per cent were living and well.

Sufficient time has not elapsed for a true evaluation of this procedure. While these results are indeed excellent, they are not significantly better than those following radiation therapy in cases of similar extent. It is hoped that a few qualified clinics will continue the surgical approach until time will permit a comparison of results. In the meantime it is suggested that the rank and file of those who treat cervical cancer not abandon radiation therapy. There is little doubt that the general adoption of the radical operation would result in needless mortality and morbidity.

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CHANCER AND CARCINOMA OF CERVIX, SIMULTANEOUS OCCURRENCE ON OPPOSITE LIPS

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CHANCRES of the cervix undoubtedly occur more frequently than the literature would have us believe. The recognition and diagnosis of such lesions, however, is certainly uncommon when compared with the frequency of primary lesions of the external genitals. The simultaneous occurrence of both chancre and carcinoma on separate cervical lips is unquestionably a rarity. In a fairly extensive review of the literature and upon questioning numerous gynecologists and syphilologists, we have been unable to find a parallel case. Because of this apparent rarity as well as to emphasize the importance of an accurate etiological diagnosis of cervical erosions and ulcerations, the following case is reported.

Case Report

Mrs. C. O., aged 48 years, was first seen (E.P.S.) on Aug. 22, 1946, with a chief complaint of vaginal bleeding. This had persisted since the onset of an apparently normal period which began July 27, 1946. Essential aspects of the history were as follows: menses began at the age of 14 years and were of the 28 to 30 day type with a seven-day flow. The patient denied syphilis and gonorrhea by name and symptomatology, although several suspicious sexual exposures had occurred within the past two months. Previous serologic tests for syphilis were negative. The patient had had two pregnancies, both of which had terminated normally—one sixteen and the other fourteen years ago.

Physical examination revealed an obese individual appearing of about the stated age, and in apparent good health. A complete physical examination was essentially normal with the exception of the pelvis. Pelvic examination revealed normal distribution of pubic hair and entirely normal external genitals. There was no evidence of cutaneous or mucosal lesions about the external genitals. The perineum was relaxed. A small asymptomatic cystocele was noted, and the cervix felt large and soft to the palpating fingers. The uterus was normal in size, shape, position, and consistency, and was freely movable. No abnormal masses were felt in the adnexa, and no parametrial induration or fixation was felt. There was moderate bleeding following digital examination.

Inspection of the cervix revealed an ulcer, 1 cm. in diameter, on the anterior lip covered with a grayish membrane. Following mechanical cleansing slight bleeding was observed from this ulcerated area. The edges of the ulcer presented no more induration than the cervix elsewhere. The anterior lip exclusive of the ulcer was pale and edematous. The posterior lip revealed a hypertrophic and slightly fungating ulceration from which slight bleeding was observed.

From the appearance of the lesion on the posterior lip, a tentative diagnosis of carcinoma was entertained. It was felt that the ulceration of the anterior lip was a separate entity and, although a definite diagnosis was not made, the resemblance to primary syphilis was noted, and such a diagnosis was given serious consideration. A serologic test for syphilis was made at this time but no dark-field examinations were done.

On Aug. 26, 1946, biopsies were taken from both lesions. Because of technical difficulties at the time, frozen sections, as requested, were not done. Serologic tests were repeated. Two days later, positive Kahn tests were reported from two different laboratories, and the patient was then sent for the first time to a syphilographer (A.B.L.) for examination and dark-field examination. This examination revealed numerous *treponema pallida* from the ulcer on the anterior lip. No other type of spirochetes were observed. Further serologic tests were made at this time which included Kahn and Kline tests. Both were strongly positive.

a 20 by 20 cm. we only lose one roentgen, so that with that slight difference we prefer to use a large field where we can get homogeneous radiation into the pelvis. If we apply this was 4,500 radium hours we are getting a dose somewhere in the neighborhood of seven erythema doses. If we accept the evidence of Wood, Prime, or Quimby that it takes ten erythema doses to produce resistance, we can understand why some cases respond and some do not and why the end-results are definitely proportional to the extent of the disease.

Our experience with adenocarcinoma runs in the neighborhood of two and one-half per cent. That is lower than the average.

The comparison of the five-year salvage shows that in Groups I and II the end-results are certainly as favorable as anything that has been offered to us by surgical attack. The mortality was nil. I could not agree with Dr. Meigs that we have very definite evidence that the treatment of carcinoma of the cervix is radical. Whether or not if we were to do a postradiation hysterectomy some of these people who had a recurrence five years after would have been saved, I am not in position to answer. If we look at the work of Lynch and if we follow the work of Morton I think eventually we will have the answer to that.

DR. EUGENE A. EDWARDS.—I agree with the opinions expressed by the essayist most completely. Certain statements are worthy of emphasis:

All patients with carcinoma of the cervix should be completely and adequately radiated.

The percentage of five and ten-year cures depends upon the extent of the lesion, rather than the microscopic characteristics of the tumor tissues. Therefore the percentage of cures will be the direct result of the establishment of the diagnosis of early localized carcinoma. The early diagnoses of cancer of the cervix are made in patients who are examined routinely and by a routine biopsy of all suspicious lesions.

Education of the public has aided in a higher percentage of cures.

X-ray therapy may or may not kill cancer cells in distant pelvic lymphatics.

The surgical treatment of carcinoma of the cervix, as the essayist has indicated, is receiving increased attention, and several groups are treating selected cases in this manner. Such management by a few well-chosen groups is justified in the light of the more recent advancements in surgical techniques, and pre- and postoperative management, such as chemotherapy and blood transfusions.

The procedure should be done only by those groups who have a large number of such patients and that can follow these patients and can present to us their results.

The management of the hopeless cancer still remains a difficult problem. It is our opinion that the cancer patient who has received adequate treatment and has recurrences is entirely a medical problem, and not a surgical one. We believe that too many of these people have unnecessary surgical operations. Palliation is the treatment of choice. Morphinism should be prevented.

Dr. Kimbrough advocates waiting six weeks after the completion of the x-ray therapy before applying radium. We have not considered such a period of time as necessary, and, in fact, have believed the sooner the radium was applied, the better. I would like to ask the reason for the delay.

DR. KIMBROUGH (Closing).—The reason for the delay of six weeks in giving radium treatment following the completion of the x-ray cycle is an attempt to avoid untoward reactions in the bladder and lower bowel. We were having so much difficulty with immediate proctitis and late rectal strictures, and so many atrophic ulcers of the bladder that we decided to adopt this interval. We believe we have lowered the incidence of these sequelae.

Fig. 1.

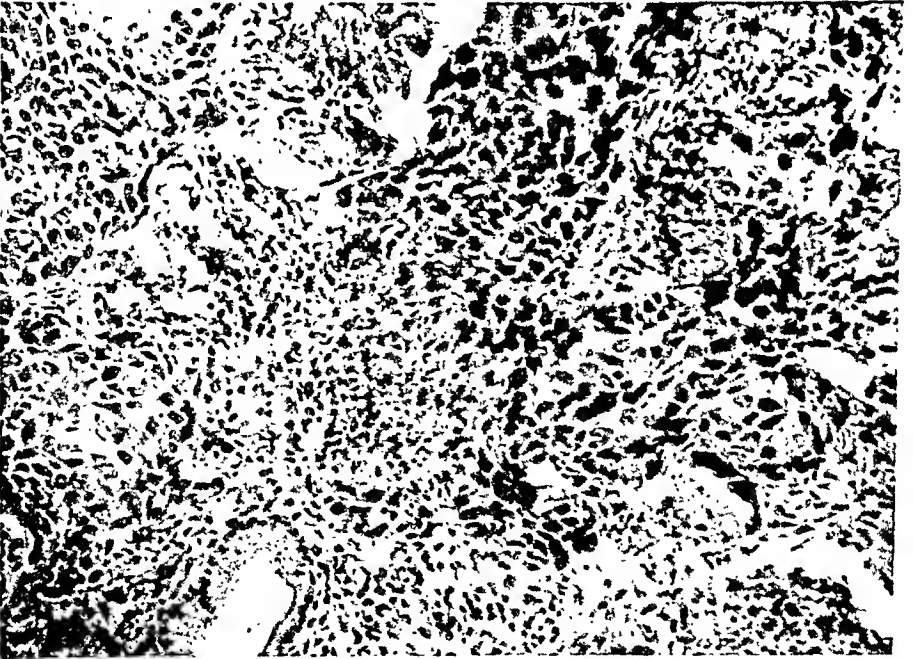
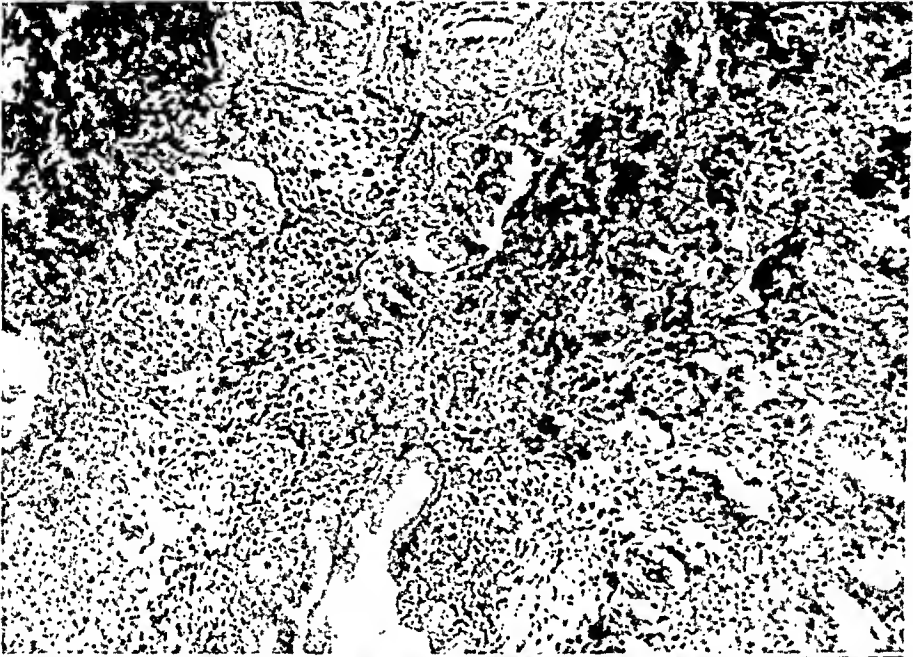


Fig. 2.

Fig. 1.—Photomicrograph of tissue taken at biopsy from posterior lip of cervix showing Grade II squamous cell carcinoma. $\times 100$.

Fig. 2.—Higher power of section of the carcinoma. $\times 400$.

Antisymphilitic therapy was commenced immediately. On Aug. 31, 1946, the pathologic report revealed a squamous cell carcinoma of the posterior lip and syphilis of the anterior lip. There was no concomitant evidence of syphilis in the material taken from the posterior lip. A complete pathologic report furnished us by Dr. Harold Gordon follows:

"*Microscopy*: The sections consist of several biopsies of the cervix uteri showing two unrelated lesions.

"Some of the fragments are almost completely replaced by granulation tissue, only a few cervical glands and a small portion of mucous membrane being visible. There is extensive ulceration of the surface. The base and margins of the ulcer consist of vascular granulation tissue with swelling and proliferation of the vascular endothelium; with severe arteritis of some of the older vessels; with confluent perivascular mantling of monocytes, fibroblasts, lymphocytes, and plasma cells; and with diffuse inflammation extending into the periphery. These changes are quite characteristic of a primary chancre.

"Other portions of the cervix show invasion of some of the glands and adjacent tissue by squamous cell carcinoma. The carcinoma cells are hyperchromatic and vary in size, but are comparatively well differentiated. There is fibrosis about some of the cancer cell nests and the blood vessels are thick walled, suggesting that the cancer probably was preceded by prolonged irritation and low-grade chronic inflammation.

"*Diagnosis*: Squamous cell carcinoma of cervix (Grade II). Primary chancre of cervix."

The patient was hospitalized on Sept. 5, 1946, for continuation of her treatment for syphilis and radium therapy. On Sept. 6, 1946, she was given 5,000 milligram hours of radium. Total antisymphilitic therapy consisted of 6,000,000 units of penicillin (60,000 units every three hours) 240 mg. of Mapharsen, and 0.39 Gm. of bismuth subsalicylate. Subsequently, the patient received 20 deep x-ray exposures to the four pelvic portals and intravaginally for a total of 6000r units. On Feb. 7, 1947, a cerebrospinal fluid examination was done which was negative throughout. This included a Wassermann, colloidal gold, globulin, total protein, and cell count. The patient's condition gradually improved and her serologic tests gradually became negative and have remained so. Two postirradiation biopsies were done, the last on Sept. 25, 1947, and neither showed any evidence of residual malignancy.

Historical

Gellhorn and Ehrenfest¹ stated that Gosselin in 1843 is reputed to have first called attention to the fact that ulcerations of the cervix may result from syphilis. A year later Bennet described the typical Hunterian chancre of the vaginal portion of the cervix. The recognition of the cervical chancre as a definite pathologic lesion, however, dates from the excellent observations of Fournier in his *Leçons* written in 1873. Gellhorn² found many reports of chancres of the cervix prior to 1905. In that year, however, Schaudinn's discovery of the spirocheta pallida demanded greater accuracy in diagnosis, and thereafter fewer reports appeared. Although dermatologists have contributed largely to our knowledge of syphilis, it is gratifying in passing to mention that Paschen, a gynecologist, was the first to confirm Schaudinn's discovery by demonstrating treponema pallida in a cervical chancre.

Discussion

Most series presented in the literature of chancre of the cervix comprise comparatively few cases, and the incidence has been variously estimated from 1 to 10 per cent of all cases of syphilis in women. This seemingly low incidence is almost undoubtedly an underestimate, for syphilologists and gynecologists alike readily admit that in many cases of frank secondary syphilis in women the primary lesion is overlooked. It is difficult to conceive of so many cases of secondary syphilis without the patient having primary lesions at some time. Excluding the external genitals and extragenital chancres (about 10 per cent) the most likely location of such a lesion is the cervix. According to Wile,³ such lesions should be very common, since the chancre in men is most frequently situated at or near the distal portion of the male organ, and infection usually occurs during coitus.

The exact anatomic location of chancre of the cervix has been variously described. Guerriero,⁴ in reporting twenty-seven cases, found the lesion surrounding the external os in 55 per cent. The anterior lip alone was involved in 30 per cent, and the posterior alone in 15 per cent. Stookey⁵ expressed the opinion that the lesion tends to be disposed away from the external os, whereas others have found the anterior lip alone predominantly involved. Thus every portion of the cervix must be looked upon suspiciously for harboring such a lesion.

Judging from cases reported in the literature, the clinical appearances of chancres of the cervix differ so greatly that no distinctive features can be taken as affording a positive naked eye diagnosis. In size, they have been described as varying from a small flat erosion to a large hypertrophic, fungaceous mass nearly filling the vagina. In appearance, there may be the small erosion, a deep ulceration, a diphtheritic ulcer, or the vegetative mass highly suggestive of malignancy. In all of these various types there most often occurs the so-called "cold edema" of the cervix, produced by an outpouring of lymphocytes into lymphatic spaces with little if any extravasation of serum. Stookey,⁶ in studying primary syphilitic lesions, has been particularly impressed with this edema and has stated that such edema, with or without ulcerations, may be the sole clinical manifestations of chancre of the cervix. This is especially true when a previously healthy cervix is infected. These cervixes appear swollen, pale pink, soft, and doughy in consistency. The induration, which is a classic feature of chancres elsewhere, is of little or no value in the cervix, as this organ is normally firm to the examining finger.

Simple erosion and carcinoma cannot be positively differentiated from chancre of the cervix except by dark-field examination and/or examination of tissue. In a noteworthy and exhaustive study by Gellhorn and Ehrenfest in 1916, they regarded such differentiation as by far the most important problem connected with syphilis of the female genitals, and this belief must be maintained. A. S. Warthin⁷ stressed the similarity of carcinoma and chancre of the cervix, and contended that it was impossible to make the differentiation by gross examination. Over a six-year period, eight cases of chancre of the cervix were sent to the University of Michigan Laboratory that were not suspected clinically. One was a uterus removed for supposed carcinoma, four were cervixes amputated, and the remaining three were biopsies for suspected malignancy. In all cases, the correct diagnosis could have been established by dark-field examination and surgery avoided. To appreciate the gross similarity of chancre of the cervix and carcinoma, it is of interest to quote in part Dr. Warthin's description of one of the cases of chancre: "it (the cervix) was enlarged, indurated, irregularly nodular or cauliflower-like, its surface showing shallow ulceration covered with a thin grayish membrane about the size of a silver dollar, completely encircling the external os, but more nodular on the anterior lip. It involved the entire vaginal portion. The consistency was very hard without crumbling—."

It has been known for some time that syphilis is not infrequently a precursor of carcinoma, i.e., carcinoma may develop upon a previous syphilitic glossitis, and cutaneous gummata have likewise been the original seat of subsequent carcinomatous transformation. In the case herewith reported, no such thing occurred, however, for the original lesion in the first place was a chancre, and then again was anatomically separated from the carcinoma by apparently normal cervical tissue. It is further recognized that any open ulcerative area is fertile soil upon which a chancre may develop, but this was likewise not true. The lesions in the cervix in this case were not only clinically distinct and separate entities, but there was likewise no histologic evidence of chronic infectious granuloma in the malignant area. The possibility of autoinoculability of chancre superimposed upon the carcinoma was likewise similarly excluded by the above.

Diagnosis

A high index of suspicion by both gynecologists and obstetricians is the prime requisite for the diagnosis of chancre of the cervix. Such a diagnosis, although a clinical suspicion, is confirmed only by a positive dark-field examination for the *treponema pallida*. Regional adenopathy is rarely of aid in diagnosis, and the so-called satellite bubo, so characteristic of

Fig. 3.

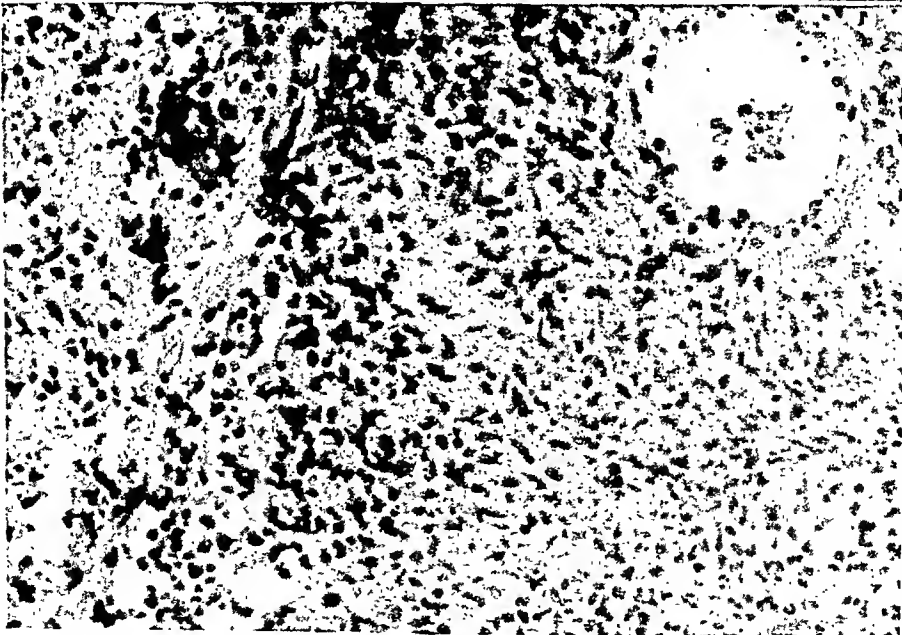
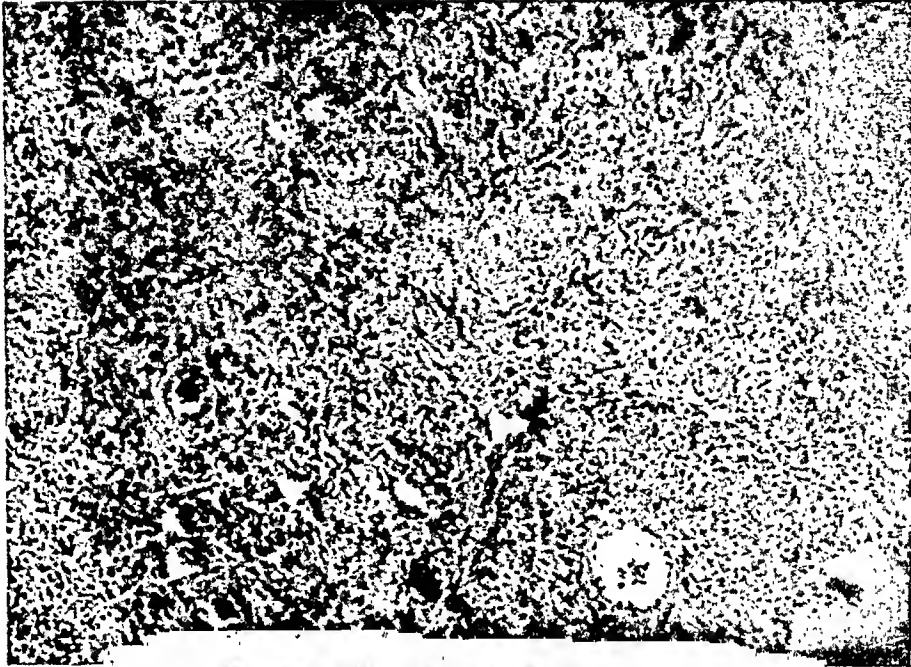


Fig. 4.

Fig. 3.—Photomicrograph of tissue taken at biopsy from ulcer on anterior lip showing chancre. $\times 100$.

Fig. 4.—Higher power of section of chancre. $\times 400$.

CHANGING TRENDS IN CESAREAN SECTION*

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A STATISTICAL study of cesarean section at Morrisania City Hospital from 1929 to 1937¹ and a related analysis of unengaged vertex presentations in full-term primiparas² revealed that the maternal and fetal mortality could be reduced by broadening the indications for cesarean section without increasing the incidence for this operation to abnormal levels. When these papers were published, the cesarean incidence was 0.8 per cent, one of the very lowest in New York City.

Since that time, ten years have passed. The staff is more experienced and better able to evaluate the cases. The x-ray has come to be of great assistance in helping to differentiate types of fetopelvic disproportion. Antibiotics are available in adequate amounts. Blood transfusions are administered freely, with less danger of reactions. All these factors must influence the mortality and morbidity rates. Accordingly, another study of cesarean section was undertaken, covering the years 1938 to 1945, inclusive, to determine if the expected improvement had been accomplished.

The total number of deliveries during this latter period is much less than in the first report (Table I), but the number of cesarean operations has increased from 112 to 127, making an incidence of 1.5 per cent. This incidence is almost double that of the first report. The increased cesarean incidence is compensated for by a reduction in the maternal death rate from 10.7 per cent to 3.3 per cent. It is interesting to note that the over-all maternal death rate has also dropped from 5.3 per thousand terminated pregnancies to 2.3, indicating a general improvement for the entire service. As will be seen, the better results with cesarean section undoubtedly played a large part in accomplishing this improvement.

TABLE I

| | 1929-1937 | 1938-1945 |
|---|---------------|--------------|
| Total deliveries | 14489 | 8356 |
| Maternal deaths per 1000 terminated pregnancies | 5.3 | 2.3 |
| No. of cesarean sections | 112 | 127 |
| Incidence of cesarean section | 0.8 per cent | 1.5 per cent |
| No. of maternal deaths | 12 | 4 |
| Maternal mortality rate, cesarean section | 10.7 per cent | 3.3 per cent |

The indications for cesarean section are listed in Table II. For the purposes of discussion each indication will be treated separately, with the exception of the minor indications. In this way, it is to be hoped that the major changes which have taken place will be clearly brought out.

*Presented at a meeting of the Bronx Obstetrical and Gynecological Society, March 22, 1948.

chancres elsewhere, is seldom if ever seen in cases of chancre of the cervix. The reason for this is the fact that cervical lymph drainage is to the deep iliac, hypogastric, and pararectal glands, although occasionally some minimal inguinal adenopathy may result from anastomosis of these and parametrial glands. Pain, either spontaneous or to touch is not present, and the lesion frequently causes no disturbance of any sort. Leucorrheal discharge is dependent upon the size of the lesion and varies in amount from slight to considerable, and is usually seropurulent in character. Contact bleeding may be a symptom.

Summary and Conclusions

1. A case of chancre and carcinoma occurring simultaneously and upon opposite lips of the cervix is reported. To our knowledge no parallel case has been reported in the literature.

2. The diagnosis of chancre of the cervix is a laboratory diagnosis, but the recognition of such cases depend upon a high index of suspicion and the more frequent use of the dark-field microscope.

3. Dark-field examinations of the cervix should be performed upon all women with secondary syphilis upon whom no primaries can be demonstrated. Likewise, all cervical erosions or ulcerations whose etiology is not apparent in sexually active females should have a dark-field examination for syphilis.

4. Syphilis of the cervix if not treated may cause a partial stenosis of this organ leading to cervical dystocia in labor.

We wish to thank Dr. J. R. Blumenthal for the original pathology report and Dr. Harold Gordon for a subsequent report and for preparation of the photomicrographs.

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Note.—Since submission of this report, the patient has been seen regularly. On May 13, 1948, cervical biopsies were negative and no clinical or laboratory evidences of residual malignancy or syphilis were demonstrable.

an ample pelvis and average-to-small babies, who really have no disproportion and in whom the presenting part can be Müllerized into the pelvis, are permitted to labor as would any patient with an engaged head.

Patients who do not fall into either of the above categories are cases of relative disproportion. Most of them will also deliver per vaginam but it is often difficult to choose the ones who will do so, without ending in a difficult forceps delivery and a badly mauled mother and baby. It has been our experience that the fetal mortality rises as high as 41.6 per cent if these cases are not delivered within forty-eight hours of labor.

Unless contraindications for a test of labor exist, such as symptomatic heart disease, tuberculosis, toxemia of pregnancy, elderly primipara, patients with relative disproportion were given a test of labor which was not to exceed twenty-four hours. If the membranes were ruptured that length of time and progressive labor had not set in, a cesarean section was done. If the cervix reached four-finger dilatation within the twenty-four hour period and the head was not engaged shortly thereafter, a cesarean section was done at that point and not at the end of twenty-four hours. Failure of the cervix to dilate steadily in that time was also grounds for doing a cesarean section.

The facts indicate that we have made no radical departure from our original attitude toward cephalopelvic disproportion. This is best judged by the number of elective cesarean sections. There were only 17 elective sections in the last study as compared to 13 in the first report.

The most striking statistical finding is the drop in maternal mortality from 12.9 per cent to zero in this group. We attribute this improvement to the type of operation and to the use of antibiotics, all of which will be discussed later.

The only stillbirth in this last series occurred when the routine, as outlined above, was not adhered to. The patient was a primipara at full term, admitted with a history of ruptured membranes for thirty-two hours and irregular pains. The cervix was 1½-fingerbreadths dilated and thick. After twenty-four hours' observation, the question of disproportion arose. X-ray pelvimetry was then done, which disclosed a true conjugate of 9.5 cm. and the presenting vertex unengaged. A low-flap cesarean section was performed. The amniotic cavity was infected. The baby was delivered in poor condition and died a few minutes later. The patient ran a stormy course, complicated by a disruption of the abdominal wound that was successfully repaired, and a pelvic abscess which was drained through the vagina. Eventually she made a complete recovery. This case occurred before the use of antibiotics.

Previous Cesarean Section

The number of cesarean sections in this group has practically doubled, which is to be expected as the hospital grows older. Every precaution was taken to operate upon these women under the best possible conditions. 30 of the 35 cases were elective cesarean sections. The remaining 5 cases were in labor from six to twelve hours and one had ruptured membranes for over twenty-four hours before admission. There was no maternal mortality.

Three babies were lost: one at the time of operation, one seven hours post-operatively, and the third died twenty hours after birth. This fetal mortality emphasizes the need for caution in guaranteeing a live baby by means of cesarean section.

Placenta Previa

The number of cesarean sections for placenta previa have almost doubled. This has been due to the inclusion of more cases of partial placenta previa and an occasional case of marginal placenta previa.

During the years covered by the first report, it was our policy to treat all cases of central placenta previa by cesarean section. Our attitude is still the same.

TABLE II. INDICATIONS FOR CESAREAN SECTIONS

| | 1929-1937 | | 1938-1945 | |
|-------------------------------|-----------|-----------------|-----------|-----------------|
| | CASES | MATERNAL DEATHS | CASES | MATERNAL DEATHS |
| Cephalopelvic disproportion | 47 | 6 | 44 | 0 |
| Previous cesarean section | 19 | 1 | 35** | 0 |
| Placenta previa | 19 | 2 | 34 | 3 |
| Premature separation placenta | 10 | 2 | 7 | 1 |
| Obstructing tumor | 6 | 0 | 2** | 0 |
| Toxemia of pregnancy | 1 | 1 | 3 | 0 |
| Cardiac disease | 4* | 0 | - | - |
| Other indications: | 7 | 0 | 4 | 0 |
| Ruptured uterus | 2* | 0 | - | - |
| Previous attempted delivery | 1 | 0 | - | - |
| Vaginal stenosis | 1 | 0 | - | - |
| Cervical stenosis | 3 | 0 | - | - |
| Previous stillbirths | - | - | 2 | 0 |
| Condyloma acuminata | - | - | 1 | 0 |
| Transverse presentation | - | - | 1 | 0 |
| Totals | 112 | 12 | 127 | 4 |

*1 case included in group of previous cesarean section.

**1 case included in group of placenta previa.

Cephalopelvic Disproportion

More than one-third of all the cesarean sections were done because of this indication. It will always be so, because cephalopelvic disproportion is one of the most troublesome problems that confronts the obstetrician.

At least 10 per cent of all primiparas are admitted with an unengaged presenting part, and while 90 per cent of these cases will eventually deliver vaginally, it takes keen judgment to determine which will do so with least injury to the mother and her baby. The incidence of cesarean section in this group can be very high, indeed, if one adopts a strict attitude of operating on any such case if the membranes have been ruptured six hours or the head is not engaged within six to twelve hours of active labor. Such criteria will increase the cesarean incidence to 4 per cent or more and the maternal mortality emanating from such centers will of course be very low because of the excellent conditions under which such patients are operated upon. We are not in accord with this policy.

TABLE III. TYPES OF CEPHALOPELVIC DISPROPORTION

| | NUMBER CASES | MATERNAL MORTALITY | NUMBER CASES | MATERNAL MORTALITY |
|-----------------------------|--------------|--------------------|--------------|--------------------|
| Cephalopelvic disproportion | 47 | 6 (12.9%) | 44 | 0 |
| Absolute disproportion | 11 | 0 | 18 | 0 |
| Relative disproportion | 36 | 6 | 26 | 0 |
| Elective cesarean sections | 13 | 3* | 17 | 0 |

*2 died of peritonitis, 1 died of postoperative pneumonia.

Cephalopelvic disproportion should be recognized immediately on admission to the hospital. In a ward service such as ours, the problem first confronts the intern staff, who are least experienced in obstetrics. The subject of unengagement, therefore, is constantly stressed at daily rounds in order to keep the intern alerted to this physical sign. He in turn notifies the resident, and, if the diagnosis is verified, an immediate x-ray pelvimetry is done and a member of the Attending Staff called. Cases of absolute disproportion are immediately operated upon, unless a fetal anomaly is known to exist. Those patients with

was brought out that the sulfonamide may have contributed to the additional renal damage and turned the table against her recovery.

Obstructing Tumors

With the exception of cervical fibroids, tumors obstructing the pelvis offer no surgical dilemma as to the method of therapy, except for the technical difficulties which may be encountered. Cervical fibroids may become very troublesome by preventing adequate lochial drainage, especially if the fibroid is located on the posterior cervical wall. Blockage of the lochia may lead to a breakdown of the uterine incision and consequent peritonitis. The two cases in the last series were treated by cesarean hysterectomy to avoid any such complication. One fibroid bulged forward so far as to prevent closure of the incision in the anterior wall of the lower uterine segment.

Toxemia of Pregnancy

We have routinely treated eclampsia and hypertensive toxemia of pregnancy according to a modified Stroganoff regime, followed by induction of labor. In the first study, a severely convulsive primipara, who failed to respond to this treatment, was sectioned but died in coma in twenty-four hours. The baby was born dead.

Three cases of toxemia were sectioned in the current group. One was a para vi, gravida vii, aged 38 years, with a long-standing hypertension. A cesarean section was done because a sterilization of the tubes was necessary. The second case was that of a pre-eclamptic, at term, not in labor, also a multipara who required tubal sterilization. The third case was a primipara, aged 13½ years, who was admitted in severe pre-eclampsia and went into convulsions while receiving the Stroganoff regime. She was watched for four days without improvement. A Watson induction was unsuccessful. She was delivered by cesarean section of a living baby and then recovered.

The vast majority of our toxemia cases are still being treated conservatively. Toxemia in this community is mainly a disease of the poorer classes. The admissions to Morrisania City Hospital are mainly from this group and it is not unusual for two or three such cases to be under observation in our antepartum room at all times. Three cesarean sections in eight years (2 of which were done, not because of the toxemia, but because of the tubal sterilization) are a small percentage indeed. All of our toxemias are now under study to determine whether the end results justify a continuance of our conservative policy.

Cardiac Disease

Four cardiac patients were treated by cesarean section in our first report, three of which sections were for the purpose of doing a sterilization operation. There were no cardiac patients sectioned in this second report because the tubal sterilization operation is performed during the postpartum period, as advocated by Fred L. Adair and Ira Brown.³

It is our opinion that cesarean section should not be done for cardiac disease per se, provided conditions prognosticate a normal delivery. On the other hand, no cardiac patient should be given a trial of labor in the presence of a possible disproportion.

Other Indications for Cesarean Section

These consisted of two instances in which the patients had had previous stillbirths resulting from difficult labors due to borderline pelvis: one patient

TABLE IV

| | 1929-1937 | 1938-1945 |
|--------------------------|-------------------|------------------|
| Placenta previa | 19 | 34 |
| Maternal deaths | 2 (10.5 per cent) | 3 (8.8 per cent) |
| Central placenta previa | 15 | 10 |
| Partial placenta previa | 4 | 16 |
| Marginal placenta previa | 0 | 8 |
| Stillbirths | 1 (premature) | 3 (1 premature) |
| Neonatal deaths | 5 (premature) | 5 (3 premature) |

The other varieties of placenta previa, however, were delivered vaginally, except for an occasional case of partial placenta previa that was bleeding too actively on admission. The fetal mortality, even after correction for prematurity, and the maternal morbidity were much too high and brought about the adoption of the following attitude; namely, that every proved case of placenta previa is to be treated by cesarean section unless the vaginal examination reveals that delivery per vaginam can be accomplished without too much risk to the mother and baby. The occurrence of active bleeding and a thick, incompletely dilated cervix in a primipara were considered sufficient cause for cesarean section, no matter what the type of placenta previa and the state of viability of the baby. Multiparas with soft, partly dilated cervix and intact membranes were treated in a manner very similar to mild instances of premature separation of the placenta; i.e., by rupture of the membranes and administration intramuscularly of small amounts of pituitrin. In fact, we look upon symptomatic placenta previa as merely a premature separation of an abnormally situated placenta.

The maternal mortality is still high (8.8 per cent as compared to 10.5 per cent in the earlier study). Two deaths were due to peritonitis at a time when antibiotics were still not available for civilian use. The third death resulted from hemorrhage, the patient being practically exsanguinated on admission.

Premature Separation of Placenta

In the first study we stated that "the Dublin method (of treatment for premature separation of placenta) should be used only where blood transfusions can be readily obtained and where trained personnel is available. Lacking such facilities, the interest of the patient is best served by a cesarean section." This policy has been carried through into the second study.

TABLE V

| | 1929-1937 | 1938-1945 |
|-------------------------------|-----------|-----------|
| Premature separation placenta | 10 | 7 |
| Partial | 3 | 4 |
| Complete | 7 | 3 |
| Maternal deaths | 2 | 1 |
| Stillbirths | 7 | 3 |
| Neonatal deaths | 2 | 1 |

There was one maternal death whose case history is given briefly in order to bring out an important lesson. A primipara, aged 36 years, was referred to the hospital at term with severe pre-eclamptic toxemia and a complete ablation of the placenta. An immediate cesarean section was done, a stillbirth delivered, the uterus was packed, 5 Gm. of sulfanilamide were instilled into the peritoneal cavity, and the patient transfused with 2,000 c.c. of blood. She went into uremia and died in 4 days. In discussion of this case at one of our conferences, it

TABLE VII. EFFECT OF ANTIBIOTICS ON CESAREAN MORTALITY

| | NO ANTIBIOTICS | | ANTIBIOTICS { SULFONAMIDES, 48 CASES PENICILLIN, 2 CASES S AND P, 7 CASES | |
|-----------|----------------|-----------------------------------|---|----------------|
| | CASES | MATERNAL DEATH | CASES | MATERNAL DEATH |
| Classical | 13 | 1 (Peritonitis) | 19 | 1 (Uremia) |
| Low flap | 54 | 2 (1 Peritonitis 1 Hemorrhage) | 37 | 0 |
| Waters | 2 | 0 | — | — |
| Porro | 1 | 0 | 1 | 0 |
| Totals | 70 | 3 | 57 | 1 |

sulfonamide was adequate and was maintained for three days, after which, if any further sulfonamide therapy was needed, it was given orally or intravenously. A few of these patients have had a repeat cesarean section and, in some instances, there were thick and extensive adhesions of the lower portion of the uterus to the anterior abdominal wall. This adhesive reaction was far more extensive than that attributable to a local peritonitis. Others have described the same findings and, for that reason, we are inclined to feel that in these particular cases the adhesions are related to the introduction of the sulfanilamide intraperitoneally.

Earlier in the text, a case was described in which a cesarean was done for complete separation of the placenta in a severe pre-eclamptic. This patient received a sulfonamide intraperitoneally and subsequently went into coma. It is felt that the sulfonamide may have added to the patient's difficulties through additional renal damage. We had another case in which the patient was sulfasensitive and almost died because of an allergic reaction.

These experiences with sulfonamides have influenced us away from the further use of them, more particularly since the advent of penicillin. In this report, only two patients received penicillin alone. However, we have continued to use penicillin intramuscularly as a routine ever since, with equally good results as with sulfonamides and without the sulfonamide reactions.

Summary and Conclusions

A review of the cesarean sections at Morrisania City Hospital from 1938 to 1945 reveals a reduction of maternal mortality to 3.3 per cent as compared to 10.7 per cent in a previous review.

The incidence of cesarean section has increased to 1.3 per cent as compared to 0.8 previously. The increased number of cesarean sections occurred mainly in the groups of cephalopelvic disproportion and placenta previa.

The reduction in maternal mortality is attributed to the predominant use of the low-flap operation, the routine use of antibiotics, improved technique of operation, and an attempt to prevent procrastination by properly evaluating labor at the time of admission. It is believed that a continuation of this policy will bring about a further reduction in the maternal mortality rate without adding to the incidence of cesarean section.

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with an extensive condyloma acuminatum involving the vulva and the vagina, in whom it was desired to avoid injury to the extensively infected soft parts, and one case of transverse presentation due to a marked hypertrophy of the anterior wall following a ventrofixation that caused an obstruction in the lower uterine segment.

There were no deaths in this group.

Type of Operation

The type of operation most commonly performed in this last series is the low-flap cesarean section. We were convinced by the first study that the low-flap operation gave the patient three times as much security against peritonitis as the classical section. It is still true.

TABLE VI. INDICATIONS AND TYPE OF CESAREAN SECTION

| INDICATIONS | TYPE CESAREAN SECTION | | | |
|----------------------------------|-----------------------|----------|--------|-------|
| | CLASSICAL | LOW FLAP | WATERS | PORRO |
| Cephalopelvic disproportion | 2 | 40 | 2 | 0 |
| Previous cesarean section | 8 | 27 | 0 | 0 |
| Placenta previa | 16 | 17 | 0 | 1 |
| | (1 died) | (2 died) | | |
| Premature separation of placenta | 4 | 3 | 0 | 0 |
| | (1 died) | | | |
| All other indications | 2 | 4 | 0 | 1 |
| Totals | 32 | 91 | 2 | 2 |
| Maternal deaths | 2 | 2 | 0 | 0 |
| Cause of death | | | | |
| Peritonitis | 1* | 1* | | |
| Hemorrhage | | 1* | | |
| Uremia | 1** | | | |

*Placenta previa.

**Premature separation placenta.

Most of the classical cesarean sections were done for placenta previa or premature separation of the placenta because opinion is divided as to which operation is preferable. The senior author dislikes invading the placental bed, which gives added maternal bleeding and fetal anoxia.

The Waters' extraperitoneal operation was attempted three times, twice successfully. The third case was discontinued when the bladder was accidentally opened. The bladder was repaired and a low-flap cesarean section done. The patient recovered with only mild morbidity.

The two Porro cesarean sections were for placenta previa complicated by large fibroid in lower uterine segment, and a case of transverse presentation that could not be delivered by internal version because of a tremendously hypertrophied anterior uterine wall resulting from previous ventrofixation.

Effect of Antibiotics

Prior to the use of antibiotics, there were two deaths from peritonitis. Since sulfanilamide and penicillin have been added to our armamentarium, there have been no deaths from peritonitis. It is our impression that these drugs have further increased the safety of cesarean section. The wound infections, seventeen (24.5 per cent) in 70 cases, not treated with antibiotics compared to 7 wound infections (12 per cent) in 58 cases treated by antibiotics.

All of the cases treated with sulfanilamide had 5 Gm. of the drug instilled into the peritoneal cavity, care being taken to avoid getting any of the powder in the abdominal wall. Within twenty-four hours, the blood concentration of

is safer from infections, gastrointestinal, respiratory, and dermal, than the infant in the crowded hospital nursery.

A point which has been emphasized by the advocates of the rooming-in arrangement is that maternal nursing is readily accepted by mothers who are interested in the advantages of the plan. This is of interest to physicians, who deplore the decline of breast feeding among American mothers.

The psychological as well as the physiological aspects of this question present important considerations. "The first (infantile) needs of the child according to present tenets, are prompt satisfaction of hunger and of the urge to nuzzle and suck, a feeling of warmth and support from nurturing mother, and a peaceful undisturbed rest between times. Accordingly, the very first traumas which can be inflicted upon the helpless infant are a refusal to give him food and comfort when the need for such is indicated, or, conversely, to force food when he is not ready or already has enough. The repetition of such traumatic situations engenders adverse reactions in both parent and child, conducive to subsequent difficulties in the guidance and training of the child."

In considering the present hospital routine separation of mother and infant, it is certain that not only the above needs of the infant have been disregarded, but the fundamental urges of the mother also have been overlooked.

This immediate postpartum period, even though short, certainly can have far-reaching effects, because mothers obviously follow the pattern of infant management as they become acquainted with it in the hospital. The present routine system, where both mother and infant are cared for as separate assignments by separate nurses and often by separate doctors, more often than not presents a somewhat baffling picture to the young mother, who, on leaving the hospital, may know little or nothing about the care and needs of her newborn. In many instances, where artificial feeding has been inaugurated, she may indeed be scarcely acquainted with her baby. A most interesting revelation during the first year's operation of the New Haven Unit has been the reaction of many mothers to rooming-in, in contrast to previous lying-in experience. They not only recalled their feeling of ignorance and helplessness on going home with the baby, but some of them expressed bitterness toward an attitude on the part of physicians who were not interested in maintaining breast feeding.

For the purposes of the present study at the Hospital, mothers were selected in the antenatal clinic, on the basis of their desire to have the baby with them after birth and the desire to nurse. Such mothers, after selection, were interviewed several times by the pediatricians associated with the project at the regular antenatal obstetric visits. At these times, the policies of the unit were explained, the plans for caring for the infant discussed, and questions encouraged. In order to aid in establishing a healthy family relationship, the husband is encouraged to be with his wife during the early part of labor and after delivery to go to the unit for a brief bedside visit. He may hold the baby at this time, after washing his hands and putting on a hospital gown. This practice may be carried out at each of his daily visits during the eight-day stay at the hospital. He may even learn diapering and aid in adjusting the baby to feeding, if the infant demands feeding while he is present.

THE ROOMING-IN PLAN FOR MOTHERS AND INFANTS*

An Appraisal From the Obstetric Viewpoint of One Year's Experience at the Grace-New Haven Community Hospital (University Service)

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ROOMING-IN is a term applied to that form of hospitalization in which the mother and newborn infant room together and the mother takes as much care of the baby as possible.¹ For purposes of study and evaluation, this plan has been carried out since Oct. 29, 1946, at the Grace-New Haven Community Hospital in a four-bed unit adapted for the purpose.

The development of the plan was a cooperative effort shared by the Departments of Pediatrics and Obstetrics and Gynecology of the Yale School of Medicine, the Yale School of Nursing, and the Grace-New Haven Community Hospital. The work of the unit is under the supervision of a committee representing these divisions.†

It may be useful to consider some of the thinking which led to the study of this plan of hospitalization. It is not a new procedure, for in certain European countries it still exists in many modern hospitals. In this country, however, this obviously natural arrangement was abandoned in favor of the hospital nursery system, which was developed to improve the standards of infant health. This improvement has been realized to a great degree. Nevertheless, it is the belief of many that the present system of separation of the infant from its mother may interfere with certain essential needs of both mother and child and that the present rigid infant-feeding schedule is a considerable factor in the background of so-called problem children.

An important contribution to the subject was made by Simsarian and McLendon,² in 1942, in a report on "The Feeding Behavior of an Infant During the First Twelve Weeks of Life on a Self-Demand Schedule." In 1945, McLendon and Parks³ published "Nurseries Designed for Modern Maternity," presenting plans for rooming-in units. More recently (1946), Maloney, Montgomery, and Trainhaur⁴ have stated, "Where mother and baby room together and the mother takes over as much care of the baby as possible, she not only satisfies her driving need to feel useful for her infant, but also, through practice and supervision in the care of the baby, diapering and bathing as well as feeding, she acquires a complete confidence in her ability to care for him and a considerable skill in doing so. She also has an opportunity to know her baby and to learn to interpret his demands for nursing care and how to meet them." These authors also state their belief that the infant, kept at his mother's side,

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†A contribution from Mead Johnson & Company has made possible the services of a full-time pediatric fellow and a full-time nursing fellow.

of the sixth week postpartum visit. According to the record, 84 patients were continuing to nurse beyond the end of this six-week period; 6 patients nursed their infants for one week or less, and all had given up because of inadequate milk supply. Forty-six patients nursed from one to six weeks. Fifteen failed to return to the clinic for obstetric check-up and in 29 there is no record as to the duration of breast feeding. In 18 of the latter, delivery was by private physicians and information has not been received from them.

There was little demonstrable effect of the Plan on the postpartum physiology of the generative tract. At the time of discharge from the hospital, 31 patients were thought to have some degree of subinvolution and in 15 of these the administration of ergotrate was ordered. Lochia was recorded as somewhat profuse in 9 patients and 2 of these passed small flecks of tissue on the fourth day. We were unable to draw any definite conclusions as to whether involution was increased or lochia was lessened in these patients over patients having the usual type of hospitalization.

During the last three months of the period covered in this review, an earlier type of ambulation was instituted in the unit. In 54 patients, who were completely ambulatory at least three days prior to their discharge from the hospital, there were no observable ill effects. In relation to unit procedure, however, early ambulation effected changes not measurable in statistical terms but nevertheless quite real. Those patients who were allowed to be up and about early in the puerperium were far more likely to feel both able and anxious to take over a considerable part of the infant care than had those whose activities had been limited by confinement in bed. In the young mother with the first child, this seems particularly desirable for reasons that have been pointed out previously.

One of the speculative aspects of the Plan has been the question of the health of the infant kept in the unit as opposed to those kept together in the newborn nursery. Our experience during this first year has been gratifying and interesting. None of the infants developed any of the usual nursery infections. One child had a number of watery stools but this condition cleared rapidly. One infant had a minor skin infection.

The primary purpose of this communication is to acquaint obstetricians with the fundamental considerations of the rooming-in plan and, from an obstetric point of view, to comment upon a year's experience with a four-bed unit. In summary the following points are supported:

1. It seems likely that there will be an increased demand for this kind of hospitalization on the part of both the laity and the profession.
2. The ways in which such demand can be met may involve changes in present hospital and nursing arrangements and in planning for new construction. Some hospitals at present are planning for both rooming-in and regular nursery care.
3. From the obstetric viewpoint, the experience at the Grace-New Haven Community Hospital does not appear to have any disadvantages as far as the health of the mother and child is concerned. Among the impor-

The New Haven Unit is so arranged that there is a complete twenty-four-hour nursing coverage. Thus, the mother is free at any time to request care for herself or the baby, when needed. The baby may be moved to the adjacent cubicle-nursery also at any time, according to the mother's desire. Visitors to the patient in the unit are restricted to two people in addition to the husband, and only one may be present at a time. Not only is the infant on a demand feeding or *ad lib* schedule, but the mother is, also, to the extent that she need not be roused for many of the usual hospital routines. The unit is attractive, quiet in atmosphere, and has a soundproof ceiling.

From the obstetric viewpoint, two things are of particular interest in reviewing the experience of this plan of hospitalization: first, the maternal nursing which has been fostered in these patients and, second, the mother and infant and family relationships which have been promoted. Recently Dr. Robert L. Jackson⁶ has emphasized six important advantages, both to the child and to the mother, in breast feeding infants:

1. Lower mortality and morbidity rates for breast-fed infants, as compared with artificially fed infants.
2. Human milk has a higher nutritional value.
3. Convenience and economy.
4. Lowered incidence of allergy.
5. Earlier involutionary processes in the mother after the termination of pregnancy and the lowered incidence of carcinoma of the breast in women who have nursed their children.
6. Emotional satisfaction, which is very important in establishing parent-child relations.

During the year ending Oct. 29, 1947, 192 mothers and 193 infants (one set of twins) were admitted to the unit. At the time of this writing, 190 obstetric records of these mothers are available for review. Of these 190 patients, 102 were primiparas, 81 multiparas, and in seven the number of pregnancies was not recorded. In studying the age groups, we find that 10 patients were 19 years or less, 133 ranged between 20 and 29 years, and 44 were in the 30- to 39-year group. Two patients were more than 40 years of age and in one instance the age was not recorded. Fifteen of the patients were Negro, the remainder white. Of the 190 patients, 122 delivered spontaneously, 57 with outlet, low, or midforceps, 6 by cesarean section, 4 by breech extraction, 1 private patient not recorded. Not all of the 190 patients had full hospitalization in the unit, because patients are admitted as beds become available after delivery. The great majority of patients (166), however, spent the entire period of hospitalization in the unit.

The review of breast feeding in the group shows that only twelve patients did not nurse their infants in the hospital. In two of these, inadequate nipples prevented nursing and in ten nursing was not desired by the patient, or was prohibited for medical reasons. In the 178 patients who did nurse their infants from birth, the length of time this was continued was variable. In the present study the concern was whether or not breast feeding had continued to the time

HISTOCHEMICAL STUDIES ON THE SECRETION OF MUCUS BY THE HUMAN ENDOCERVIX*

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THE periodicity of mucous secretion by the human endocervix is a well-established phenomenon. Séguy and his co-workers^{1, 2} reported an increase in the amount and a decrease in the viscosity of the mucus secreted by the cervix during the midportion of the menstrual cycle. Furthermore, these authors showed by the determination of urinary estrogen and by the examination of the ovaries at operation that the midcycle increase could be correlated with the occurrence of ovulation. More recently, the hormonal control of secretion by the cervix has been demonstrated by the administration of ovarian hormones to ovariectomized women (Abarbanel³). The administration of estrogen results in the copious production of clear mucus of low viscosity. Subsequent treatment with progesterone causes a decrease in the volume of mucus secreted and a concomitant increase in its viscosity.

The clinical significance of the changes in the physical and chemical properties of the cervical mucus during the menstrual cycle has been demonstrated by Lamar, Shettles, and Delfs.⁴ These authors have shown that the penetrability and longevity of spermatozoa are significantly greater in mucus obtained at the midcycle than in mucus obtained during other phases of the cycle.

The nature and extent of concurrent histologic changes in the endocervix similar to those exhibited by the endometrium have not been satisfactorily established. The opinion of Schröder⁵ that it is difficult to detect cyclic changes in the endocervix because of the great individual variability seems to be representative of the earlier workers.

More recently, however, Wollner⁶⁻⁸ has described cyclic histologic changes of an extensive nature. The method used in obtaining the tissue may have been a factor in his observations. Wollner used an electrocautery to remove strips of tissue about 4 mm. thick, several biopsies frequently being taken from the same individual during a single cycle. Subsequent study of tissue so treated in the living state does not necessarily give information comparable to that obtained from tissue removed by surgical incision. According to the observations of this author there is a complete desquamation of the surface mucosa and widespread destruction and exfoliation of the glandular epithelium during the menstrual phase. During the early proliferative phase rapid regeneration of the epithelial elements takes place, the newly regenerated epithelium being composed of low columnar cells containing relatively little cytoplasm. Throughout the remainder of the cycle the epithelial cells are said to increase in height and the glands to increase in number and size, the peak of development being reached shortly before menstruation.

*This investigation has been aided by a grant from the Jane Coffin Childs Memorial Fund for Medical Research, and by a grant recommended to the American Cancer Society by the Committee on Growth of the National Research Council.

tant advantages are a natural mother and child and family relationship, and the emphasis on the values of breast feeding, and the self-demand schedule.

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The striking histologic feature in our series of cervixes obtained at various stages of the menstrual cycle was the individual variation, particularly in the number and size of cervical glands, which was apparently unrelated to the menstrual cycle. The variability between patients in the pattern of the cervical mucosa is as marked as the extreme variability in the pattern of human mammary gland. Due to the comparatively small number of cases, no attempt has been made to study the minute cytologic detail which was recorded by Sjövall.⁹ However, evidence from our specimens agrees with the conclusion of Sjövall that there is no indication of the widespread menstrual exfoliation of surface and glandular epithelium described by Wollner.⁶⁻⁸

The results obtained from the tissue sections stained specifically for mucin are informative. At all times throughout the cycle mucin is present in the apical cytoplasm of a large majority of the cells of both the surface and glandular epithelia (Figs. 1 and 2). There seems to be relatively little variation in mucin concentration as judged by the intensity of staining. However, there is a definite variation in the amount of mucin-containing secretion present in the glandular lumina at different phases of the cycle. Luminal mucus is abundant during the late proliferative and early secretory phases. There is a considerable decrease in the amount present during the late secretory, menstrual, and early proliferative periods. This histochemical evidence of increased secretory activity during the ovulatory phase of the cycle correlates well with the gross observations of Séguéy and his co-workers previously referred to. Furthermore, the present observations tend to confirm the conclusion of Sjövall, based upon the degree of papillary excrecence exhibited by the glandular epithelium, that the peak of endocervical activity is reached at the midcycle and not during the premenstrual period as stated by Wollner.

It is also of interest to note that, unlike the goblet cell of the intestinal mucosa, no cellular destruction accompanies the release of mucous secretion in the cervix. The secretory products appear to pass through the intact free surface membrane of the cervical gland cell without an accompanying decrease in cell volume. This indicates that the elaboration and release of mucus is a continuous metabolic process during periods of active secretion. Chemical analysis has shown that not only does the total quantity of mucus increase at the midcycle, but its relative water content also increases (Pommerehne¹¹). These analytical and histochemical observations confirm the suggestion that the secretion-promoting action of estrogen may be due, at least in part, to its effect on uterine water metabolism.

During pregnancy the cervical glands increase markedly in size, so much so that the stroma of the mucous membrane is compressed into thin interglandular partitions. The apical cytoplasm of the cells of the surface and glandular epithelia and the glandular lumina contain large quantities of intensely staining mucus. This finding is in complete agreement with the observations of Wislocki and associates.¹⁰ Studies on the physical nature of the mucus during pregnancy indicate that it is not free running but forms a semi-solid plug in the cervical canal (Clift¹²). Little is known regarding the factors responsible for this change in physical character, although a clue may be afforded by the observation of Abarbanel³ that progesterone causes a decrease in volume and increase in the viscosity of cervical mucus.

After the menopause the cervical glands decrease in size and the glandular epithelium, although of the columnar type, seems to be reduced in height. In accordance with the findings of Wislocki and his co-workers, little or no mucin was present in either the gland cells or lumina of our specimens (Fig. 3). It is apparent that cervical secretion sharply decreases following the cessation of ovarian activity.

In a subsequent extensive survey of the problem, Sjövall⁹ disagreed with the findings of Wollner on two major points. First, he believed that the peak of endocervical development is reached at the midcycle and not during the premenstrual phase; second, he observed no widespread desquamation during the menstrual phase. He reported an intensive proliferation of the epithelial elements during the first half of the cycle which reaches its culmination at the time of ovulation. A partial regression was said to take place shortly before and during menstruation.

A new approach to the problem is suggested by the work of Wislocki and associates¹⁰ in which histochemical techniques have been used for the identification of mucin and other constituents of the cervical glands and their secretion. The emphasis of their study was on the nature of the substances present. Since the specimens were not timed with respect to the menstrual cycle, these authors were not concerned with the problem of cyclic change.

The present investigation was undertaken with the purpose of studying by histochemical techniques the production of mucus by the cervical glands during the menstrual cycle and to observe any correlations with the endometrial cycle.

Materials and Methods

In order to secure prompt fixation, material was obtained from patients undergoing total hysterectomy. Samples of tissue of endometrium and of endocervix were removed and fixed immediately. The microscopic study of the endometrium provides a more reliable index of the stage of the cycle than does the meager menstrual history usually given by the patient. It is almost impossible to obtain completely normal tissue from the age groups undergoing surgery. In this series all cases with cervical or endometrial lesions or with demonstrable ovarian endocrine dysfunction were rejected. Of more than 60 cases examined, only 21 are included as being normal. The majority of these uteri were taken from women in the later reproductive age group whose chief complaint was the presence of uterine fibromyomas.

The uteri were received from the operating room shortly after surgical removal. The uterus was opened and the amount of mucus in the cervical canal was estimated on a comparative basis. Cervical specimens were fixed in chilled picro-alcohol-formol (PAF) to preserve the mucin. Tissue from other portions of the reproductive tract was fixed in Bouin's fluid for subsequent diagnostic study.

The tissues were imbedded in paraffin and were sectioned at 10 micra. Sections of cervices fixed in PAF were stained by the Bauer-Feulgen technique which demonstrates the presence of both glycogen and mucin (glycoprotein). In order to differentiate these substances, parallel sections were incubated with saliva to remove glycogen before staining. To spot-check the efficacy of this method, the mucin in occasional sections was also stained metachromatically with toluidine blue. The cervical and other tissue specimens fixed in Bouin's fluid were stained with hematoxylin and eosin.

Observations and Discussion

In nonpregnant women of childbearing age the endocervical mucosa is several millimeters thick. Its surface epithelium, which may exhibit considerable folding, is continued into numerous branched glands. Both the surface and glandular epithelia are composed typically of a single layer of tall columnar cells with basally situated nuclei and clear apical cytoplasm. The glands lie in a rather dense fibrous stroma, the entire mucous membrane resting directly on the dense stroma of the cervix.

The present cytochemical observations on the production of cervical mucus are, for the most part, in close agreement with the gross and chemical findings of other authors previously discussed. However, unlike Pommerenke,¹¹ we have found no evidence of glycogen in either the surface and glandular epithelium or in the luminal mucus itself. Several possibilities exist which may account for this divergence of results: (1) the polysaccharide isolated by Pommerenke may not be glycogen; (2) if glycogen, it may be a contaminant from either the endometrial or vaginal secretions; (3) the cytochemical test for glycogen used in the present work may not be sufficiently sensitive to indicate the relatively small quantities reported to be present. That the first alternative is most probable is suggested by the observations of Shettles and Dische.¹³ These workers have found evidence that the main bulk of the polysaccharides in human cervical mucus is either identical with or closely related to one of the blood group substances.

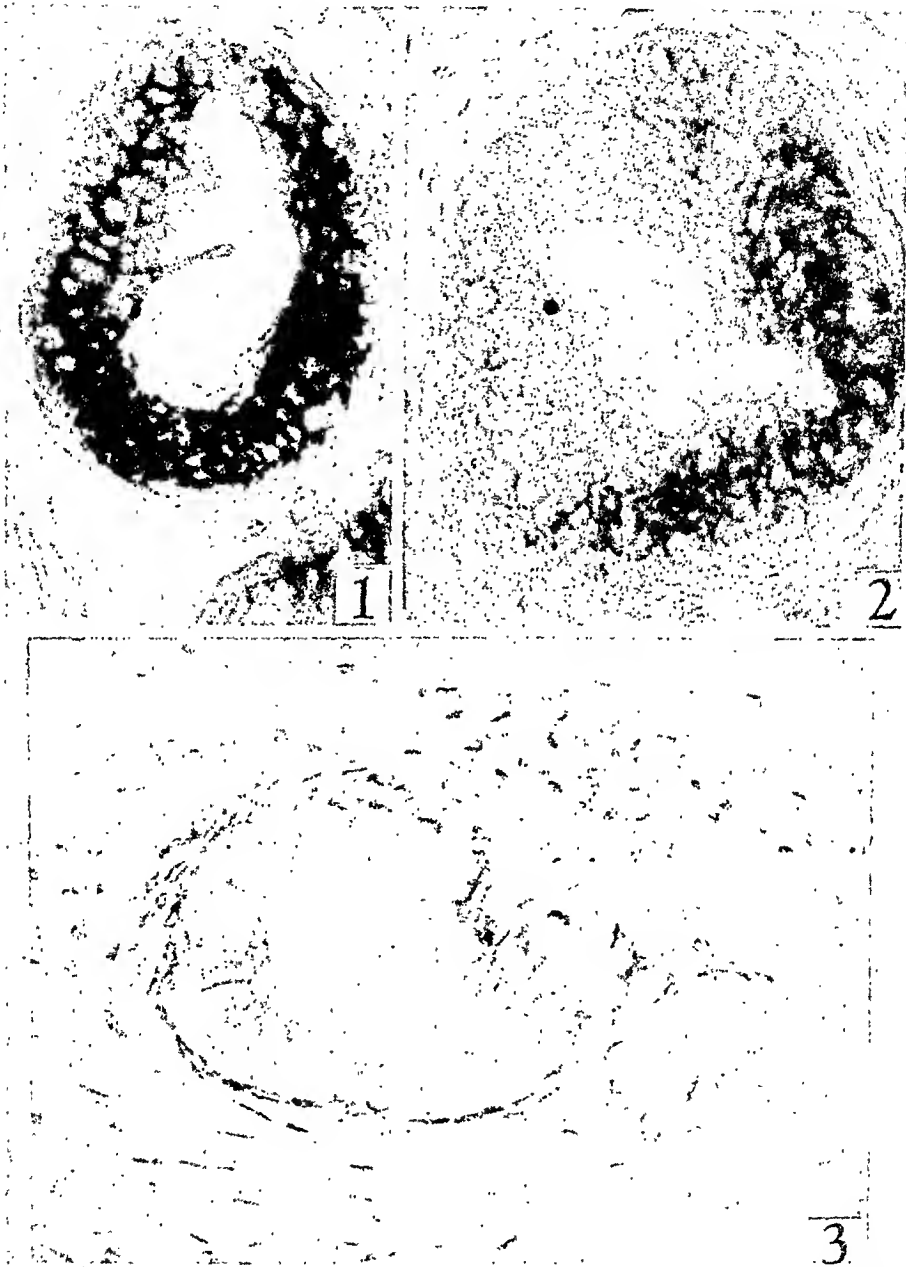
Summary

The secretion of mucin by the glands of the human uterine cervix has been studied cytochemically throughout the menstrual cycle. Relatively constant quantities of mucin are present in the apical cytoplasm of the cells of the glandular epithelium at all stages of the cycle. However, active secretion of this substance is a rhythmic process. Large amounts of mucin are liberated during the midcycle, whereas relatively little secretion is found to occur during the late secretory, menstrual, and early proliferative phases.

In contrast to the normal cyclic cervix, little or no mucin is produced in the cervixes of postmenopausal women. During pregnancy, on the other hand, there is a marked increase in the amount of mucin present.

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Photomicrographs (X 450) of transverse sections of uterine cervical glands treated by the Bauer-Feulgen method to demonstrate mucin. Cellular structure is indistinct since no other cytoplasmic counterstain has been used.

Fig. 1.—Typical cervical gland from a uterine specimen obtained on the first day of menstruation. The cytoplasm of the epithelial cells is filled with intensely stained mucin. Only traces of mucin are present in the lumen.

Fig. 2.—Cervical gland from a uterus removed fourteen days after the onset of menstruation. The endometrial diagnosis was that of late proliferative phase. Moderate to intensely staining mucin is present in both the epithelial cytoplasm and luminal secretion.

Fig. 3.—Gland from the uterine cervix of a woman whose last menstrual period occurred seven years previous to operation. No mucin staining is present.

that the cord pulsations were weak. Because of the baby's pallor, an immediate blood count was done, and this revealed a hemoglobin concentration of 8.7 Gm. per cent (67 per cent), with a red cell count of 2.5 million per cubic millimeter.

An antenatal Rh test had been performed on the mother, which showed her to be Rh positive, and this fact, together with the existence of a central placenta previa, suggested the idea that the baby might be suffering from anemia and shock due to occult hemorrhage from the fetal surface of the placenta. Fetal hemorrhage of this type would not be manifest because the fetal blood would be mixed with the maternal blood lost at the delivery. A transfusion of 120 c.c.* of citrated group A blood was given with the aid of a syringe-valve apparatus, and the infant immediately improved. The following morning a blood count revealed a hemoglobin concentration of 11.7 Gm. per 100 c.c. (81 per cent); red blood cells, 4.35 million per cu. mm.; white blood cells, 41,200 per cu. mm.; with 52 nucleated red blood cells per 100 white cells on smear. The same evening a blood count showed a hemoglobin concentration of 16 Gm. per 100 c.c. (110 per cent). This improvement was maintained, and on the following day the hemoglobin concentration was 14.9 Gm. per 100 c.c. (103 per cent); red blood cells, 4.7 million; white blood cells, 32,400; polys, 65; band forms, 10; lymphs, 19; monos, 2; eos, 4; with only 2 nucleated red blood cells per 100 white cells.

Despite the sustained improvement in blood count, the baby looked pale, and oxygen had to be administered, because the respirations became rapid and shallow whenever the oxygen therapy was discontinued. This indicated that while the blood count was satisfactory, the blood volume was still probably below normal. On the following day, August 8, the hemoglobin concentration was 13.3 Gm. (92 per cent); red blood cells, 4.55 million; white blood cells, 17,600; and a transfusion of 60 c.c. of blood was given. Following this transfusion the hemoglobin concentration rose only to 14.5 Gm. (100 per cent), but the patient improved markedly so that the oxygen therapy was no longer necessary, which confirmed the idea that reduction in blood volume was the cause of the symptoms. The patient was discharged from the hospital in good condition, and when she was seen again on August 28 she appeared entirely normal, and the blood count showed hemoglobin concentration 10 Gm. (76 per cent); red blood cells, 4.09 million; white blood cells, 18,200; polys, 33 (1 band form); lymphs, 60; monos, 3; eos, 3; with $\frac{1}{2}$ per cent reticulocytes and no erythroblasts on the smear.

As has already been mentioned, the first clue to the correct diagnosis in this case was provided by the antenatal Rh test which showed the mother to be Rh positive. The results of more complete tests performed later on are shown in Table I.

TABLE I

| BLOOD OF | GROUP AND SUBGROUP | M-N TYPE* | RH-IR TYPE |
|-------------------------|--------------------|-----------|--------------------|
| Mother | A ₂ B | N | Rh ₁ rh |
| Patient (female infant) | A ₂ | MN | Rh ₂ |

*The M-N types are not clinically significant but are included for the sake of completeness.

The second lead was supplied by the history of central placenta previa, which is usually characterized by profuse placental bleeding. In addition, physical examination of the infant showed that neither spleen nor liver were enlarged, while if such severe anemia were due to hemolysis, considerable enlargement of these organs should be present. Moreover, the ieterus index of the cord serum was only eight units. Undoubtedly, this child owes her life to the prompt and adequate transfusion therapy which she received.

CASE 2.—The patient was a newborn, full-term, female infant, weighing 6 pounds, 10 ounces, who was born at 3:15 A.M. on Feb. 8, 1947. The infant was the first born to her mother, who had never received a blood transfusion and was known to be Rh positive, group O from antenatal tests. Labor had been normal and was completed with an easy outlet forceps.

*About twice the usual dose for an infant weighing 7 pounds or less.

DIAGNOSIS AND TREATMENT OF ANEMIA OF THE NEWBORN CAUSED BY OCCULT PLACENTAL HEMORRHAGE

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THE hazards to the mother of hemorrhage caused by abruptio placentae and placenta previa are well known, but while it is generally recognized that such cases are attended with high fetal mortality rate due to asphyxia, little or no cognizance is ordinarily taken of the fact that infants born alive in such cases or even in apparently normal deliveries may be suffering from a dangerous anemia due to occult hemorrhage from the placental or umbilical vessels. One reason for this may be that such severe neonatal anemias closely simulate the hemolytic anemia of erythroblastosis fetalis, so that these infants are usually treated like erythroblastotic infants. Undoubtedly many infants who might otherwise have been saved have been lost due to failure to recognize the true nature of the condition, considering that severe posthemorrhagic anemia, which is often associated with shock, calls for much more vigorous transfusion therapy than hemolytic anemia. Now that exchange transfusion^{1, 2} has come to be used almost routinely in cases of erythroblastosis due to Rh sensitization, it is even more important to distinguish posthemorrhagic anemia, because the former is best treated by simple, massive blood transfusions rather than by exchange transfusion. The development of serologic tests³⁻⁶ whereby the presence or absence of erythroblastosis can be determined with an accuracy approximating 100 per cent has simplified this problem, especially if antenatal Rh tests are performed routinely. In cases where the mother is Rh positive, or, if Rh negative, has neither anti-Rh agglutinins nor glutinins in her serum, the diagnosis of erythroblastosis can be excluded, as a rule,* raising in its place the question of a possible posthemorrhagic anemia.

The purpose of this paper is to present cases of severe anemia of the newborn infant due to occult placental hemorrhage, and to discuss the differential diagnosis and treatment of the condition.

Reports of Cases

CASE 1.—On Aug. 5, 1947, the author was requested to see the patient, a female newborn infant, because it was noticed at delivery that the infant looked extremely pale and had very low vitality.

The mother's obstetric history was as follows: Her first pregnancy, in 1942, had terminated with a seven-month stillbirth, the cause of which was not determined. The second pregnancy, in 1944, had terminated with a full-term natural delivery of an infant weighing 6 pounds, twelve ounces, who was apparently normal and is alive and well. The patient with whom we are concerned here was the result of her mother's third pregnancy. This baby was delivered by cesarean section because of a central placenta previa, and the obstetrician noticed

*This does not take into account the possibility of A-B sensitization, or other rare sensitizations.

he belongs either to genotype R^1R^1 or to genotype R^1r' , of which the former is by far the more common and therefore the more probable. It will be noted that the living child, who recovered from erythroblastosis, belongs to type Rh, rh , in conformity with expectations. In view of these results there was hardly any doubt that the fetus the mother was carrying would also be Rh positive.

TABLE III

| BLOOD OF | GROUP AND SUBGROUP | M-N TYPE | RH-IR TYPE | |
|-------------|--------------------|----------|---------------------------------|---------------------|
| | | | PHENOTYPE | GENOTYPE |
| Father | A ₁ | MN | Rh ₁ Rh ₁ | R^1R^1 or R^1r' |
| Mother | A ₂ | MN | rh | rr |
| First child | A ₁ | MN | Rh ₁ rh | R^1r |

Tests for Rh antibodies on the maternal serum at the time of this first antenatal examination gave the following results:

Agglutination method = negative

Albumin-plasma conglutination method = negative

Thus, whatever sensitization the mother had possessed at the time of her second pregnancy had subsided in the interval of more than three years until the present pregnancy began.

The Rh antibody titrations were repeated on Dec. 20, 1946, Feb. 15, 1947, and on March 15, 1947, and at all these examinations no Rh antibodies were demonstrable in the maternal serum. The mother was being counterimmunized with typhoid and pertussis vaccines, and these results we ascribed to the successful use of the vaccines and were lulled into a false sense of security as subsequent events soon revealed.

When the patient was born on March 31, 1947 at 1 A.M., she proved to be extremely pale and feeble; she gave only one good cry and then breathed poorly. Much mucus was aspirated from her throat, and an immediate blood count showed a hemoglobin concentration of only 7.4 Gm. per 100 c.c. (58 per cent), with 3.09 million red blood cells per cu. mm.; white blood cells, 46,500; polys, 15; bands, 3; small lymphs, 58; large lymphs, 20; monos, 1; eos, 1; baso, 1; myelocytes, 1; and there were 25 erythroblasts and 17 normoblasts per 100 white cells on the blood smear. A blood transfusion was obviously urgently indicated, and this was started at 5 A.M., by which time the infant's condition was critical. After a total of 90 c.c. of group A, type rh blood were transfused, the infant died and could not be revived. In cutting down at the ankle to expose the vein for the transfusion, it was noticed that the tissues were bloodless, and the vein was found to be empty and fragile, so that only with the gentlest handling was it possible to cannulate it and start the transfusion. Physical examination revealed the spleen to be hard and markedly enlarged, and tests performed later on revealed the baby's blood type to be group O, type M, type Rh₁rh, while the icterus index of the cord serum was only 10 units. Another blood specimen was drawn from the mother at the time of delivery and this showed the presence of anti-Rh₀ agglutinin of 16 units titer. Still another specimen obtained from the mother about two weeks after the delivery showed the presence of anti-Rh₀ agglutinins of a titer of 128 units.

At postmortem examination, the characteristic findings of erythroblastosis were noted. There was marked hepato-splenomegaly with microscopic evidence of extensive erythropoiesis and some myelopoiesis. In addition, the liver cells were filled with hemosiderin pigment. Other incidental findings noted were aspiration of amniotic contents, and a small hematoma of the arch of the aorta.

This case is unusual because antenatal tests repeated at intervals up to two weeks before delivery failed to reveal the presence of any Rh antibodies, yet the infant proved to be erythroblastic. The explanation for the presence of erythroblastosis in the infant was provided by another antibody test on the maternal serum at delivery which then revealed the presence of Rh antibodies. The moral of this case is that in the face of an obstetric history of erythroblastosis in a

The infant cried spontaneously, and respirations were good at first, but it was noticed that she was very pale. There were no evident anatomical anomalies, no edema; and meconium and urine passed by the infant appeared normal. An immediate blood count showed: hemoglobin concentration, 6.5 Gm. per 100 c.c. (45 per cent); red blood cells, 2.21 million; white blood cells, 57,000; polys, 27; juveniles, 4; myelocytes, 3; lymphs, 55; eos, 2; monos, 4; unidentified cells, 3; with 59 nucleated red cells per 100 white cells on the smear.

While the diagnosis of erythroblastosis fetalis seemed to be excluded by the facts that the infant was the first born and her mother Rh-positive, this patient was seen before the infant of Case 1, and the true nature of the condition was not fully appreciated. The infant was given continuous oxygen therapy and vitamin K. At 4:30 A.M. the infant ceased breathing, but the heart action continued. Because of the infant's desperate condition, 100 c.c. of blood were drawn from the mother, mixed with 20 c.c. of Witebsky's A and B group substances, and transfused to the infant. Following this, the infant rallied, she cried weakly, and spontaneous breathing was resumed. This improvement was only evanescent, however, and at 5:30 A.M., the infant expired.

In retrospect, it seems evident that despite the apparently normal delivery, this infant was suffering from posthemorrhagic shock caused by occult placental bleeding. Had this patient been seen after Case 1, the true nature of the condition might have been recognized, and the infant might have been saved by more energetic transfusion therapy. As already mentioned, the only clues to the true nature of the condition available to us were the facts that the infant was first-born, and her mother was Rh-positive. Results of more complete blood tests performed later on are shown in Table II. Direct matching, by the agglutination and conglutination methods, of the maternal serum against the blood cells of the infant and her father showed no clumping, confirming the impression that the mother was not isosensitized. Moreover, the ieterus index of the cord serum was only four units, which further excluded the presence of any hemolytic process.

TABLE II

| BLOOD OF | GROUP | M-N TYPE | RH-HR TYPE |
|----------|-------|----------|---------------------------------|
| Father | O | MN | Rh ₁ Rh ₂ |
| Mother | O | MN | Rh ₁ Rh ₁ |
| Patient | O | MN | Rh ₁ rh |

At postmortem examination, the findings noted by the pathologist were anemia, hepatosplenomegaly, extramedullary hematopoiesis in the liver, adrenal glands and spleen, atelectasis of the lungs, and focal congestion of the viscerae. The only diagnosis ventured by the pathologist was "a newborn with anemia."

CASE 3.—This is an unusual case of erythroblastosis which is included for purposes of comparison with Cases 1 and 2, because of certain of its features which are relevant to the problem under discussion.

The patient was a female infant, born on March 31, 1947 at 1 A.M., the result of her mother's third pregnancy. The patient's mother gave the following obstetric history. Her first pregnancy terminated with an incomplete abortion which was treated by curettage on March 24, 1942. The second pregnancy yielded a full-term female child, who was born on February 18, 1943. This infant developed a hemolytic anemia and was treated by numerous transfusions of Rh-negative blood, and finally recovered completely at the age of six weeks. This child is alive and well, without any sequelae of erythroblastosis. The patient's mother was first seen during her third pregnancy on Sept. 15, 1946, when she gave her last menstrual period as June 18, 1946, with an E.D.C. of March 25, 1947. At this first antenatal examination, grouping and Rh-Hr tests gave the results seen in Table III.

As expected, these results showed the mother to be Rh negative and the father to be Rh positive. Moreover, the father was Hr negative (indicated by the designation Rh,Rh₁), so that

reported three interesting cases of vasa previa: one with stillborn baby, one with an asphyxiated baby that recovered, and one with a baby that died in a few days of anemia. Thus, where the babies are born alive, in occasional cases the babies will have a severe posthemorrhagic anemia, and such babies should be treated by massive transfusion without delay if they are to survive.

Summary

1. Attention is called to a previously unrecognized entity, namely, severe anemia of the newborn caused by unapparent hemorrhage from the fetal surface of the placenta.

2. Two cases are described of newborn infants exhibiting this picture of severe posthemorrhagic anemia, one of whom recovered following treatment by blood transfusion, while the other died despite transfusion. In both these cases the mothers were Rh positive as revealed by routine antenatal blood tests, and isosensitization was ruled out as playing any role by detailed serological tests and the absence of any icterus of the cord serum.

3. In a third fatal case of severe anemia in the newborn baby of a sensitized Rh-negative woman, the anemia was apparently due primarily to hemorrhage rather than hemolysis. The significance of this finding in relation to the treatment of such cases is that if exchange transfusions are given to such erythroblastotic babies, a margin of 150 c.c. instead of only 50 c.c. should be maintained between the amount of blood injected and the amount of blood withdrawn, in order to correct the reduction in blood volume as well as the anemia.

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previous child, one must not be lulled into a false sense of security by failure to demonstrate Rh antibodies in the maternal serum. In all such cases, the transfusionist should stand by at the delivery prepared to transfuse the infant if necessary. Apparently something must have happened in the interval of two weeks between the last antenatal examination and the delivery which caused the sudden rise of maternal Rh antibody titer and the appearance of the severe anemia in the infant. Had labor been induced two weeks before term, the outcome in this case might have been entirely different. Incidentally, this case also shows the relative ineffectiveness of counterimmunization with typhoid and pertussis vaccines in a seemingly ideal case for the application of this treatment. While there is ample experimental data to support the principle of competition of antigens, it does not seem likely to lead to an effective prophylactic treatment against erythroblastosis.

The simplest way to account for the findings in this case would be to postulate some defect on the fetal side of the placenta, appearing during the two-week interval between the last antenatal Rh antibody titration and the delivery of the patient. The leakage of the fetal blood into the maternal circulation would account for the sudden reappearance of Rh antibodies in the maternal serum. Moreover, a slow ooze of fetal blood from such a placental defect could also account for the extreme anemia and shocklike condition of the infant at birth. The main objection to this concept is the difficulty of demonstrating such postulated placental defects in pathologic specimens. However, the reason for this may be that such defects need not be large, and as a rule would probably be demonstrable only *in vivo*, as we succeeded in doing another case recently seen by us. In this other case, the baby was delivered by cesarean section, and at the operation a herniation was found of the anterior uterine wall (due to a previous cesarean section), consisting of a sac about the size of a walnut, and lined only by peritoneum and filled with blood, which ruptured upon palpation.

The importance of this interpretation is that when erythroblastic babies are born with extreme anemia and shock one must consider the possibility that the anemia may be due not merely to hemolysis but also to actual blood loss through a placental defect. The correctness of this concept as applied to the case reported here seems indicated by the normal icterus index of the cord serum. Under this concept, such infants are best treated by simple but massive transfusions of Rh-negative blood, as in a case previously reported by the writer.⁷ If exchange transfusion therapy is applied in such cases, a margin of about 150 c.c. (instead of 50 c.c.) should be maintained between the volume of blood injected and the volume of blood withdrawn, in order to correct the reduction of blood volume produced by the inapparent placental bleeding.

Comment

Related to the problem under discussion is the clinical entity known as vasa previa, a condition usually associated with a velamentous insertion of the cord. A good review of this subject has recently been published by Rucker and Tureman,⁸ who also add three new cases of their own. This complication of pregnancy is not important from the maternal standpoint, but carries with it a high infant mortality rate. Thus, in a series of 52 cases culled from the literature, as many as 58 per cent of the babies died. The babies who lived were mostly delivered through a tear in the membranes between the blood vessels without rupturing the blood vessels. The babies who died were mostly stillborn, presumably due to asphyxia from pressure on the exposed blood vessels, or from shock caused by bleeding *in utero* from the ruptured blood vessels. Caffarotto⁹

this time, bleeding had ceased, no further stilbestrol was given, but thyroid extract was administered as indicated by the basal metabolism rate determination. These patients were seen routinely forty-eight hours later, when more stilbestrol was given if indicated.

This investigation comprises well over 200 cases which were controlled satisfactorily by the use of stilbestrol as noted. In sixty cases for which adequate follow-up was available, there were definite trends which we believe are of sufficient importance to consider in detail. Of these, 74.2 per cent required only one injection of stilbestrol to control the bleeding; 9.7 per cent, two injections, and 13 per cent required three. The remaining 3.1 per cent required four or more injections with supplemental oral administration in 15 mg. doses at bedtime.

TABLE I. STILBESTROL DOSAGES

| DOSE (MG.) | NO. OF PATIENTS BY AGES | | | | TOTAL PATIENTS |
|---------------|-------------------------|-------|-------|-------|-------------------|
| | 10-20 | 20-30 | 30-40 | 40-50 | |
| 25 | 8 | 40 | 11 | 1 | 60 |
| 50 | | 4 | 2 | | 6 |
| 75 | | 5 | 3 | | 8 |
| 100 | | 1 | | | 1 |
| 125 | | | 2 | | 2 |
| 150 | | | | | |
| 200 | 2 | 1 | | | 3 |

When the time element was studied, it was noted that 42 per cent stopped bleeding in less than twelve hours and 28 per cent in less than twenty-four hours. Thus in 70 per cent of these women, the bleeding was completely controlled or diminished to a negligible quantum. While bleeding in the remaining 30 per cent was not completely controlled in twenty-four hours, it was markedly reduced in amount.

Despite the large or repeated dosage, no toxic effects were observed of sufficient intensity to cause the drug to be discontinued. Furthermore, no case of estrogen-withdrawal bleeding was encountered in this investigation. We know of no other nonoperative method which gives as favorable results, despite the fact that the approach may seem more rationally scientific.

In 37 of the 60 cases under consideration, the basal metabolic rate determinations indicated decreased thyroid function (in 27, or 70 per cent) ranging from minus 1 to minus 30 per cent. Ten were on the positive side with a similar range (plus 1 to plus 30 per cent). Twenty-three are not accounted for because of various types of patient failures which would have nullified the significance of the determinations.

TABLE II. BASAL METABOLIC RATE

| AGE GROUP | MINUS | | PLUS | |
|-----------|-------|----------|------|----------|
| | NO. | PER CENT | NO. | PER CENT |
| 1-10 | 13 | 35.1 | 6 | 16.2 |
| 10-20 | 13 | 35.1 | 3 | 8.1 |
| 20-30 | | | 1 | 2.7 |
| 30-40 | | | 1 | 2.7 |
| Total | 26 | 70.2 | 11 | 29.7 |

Classification of the types of bleeding indicated that 41.2 per cent was menorrhagic; 30.2 per cent, menometrorrhagic, and 28.6 per cent, metrostaxic.

Evaluation of 53 endometrial biopsy studies revealed that the bleeding was associated with a proliferative endometrium in 37 (70.2 per cent). Twelve

THE USE OF STILBESTROL IN ABNORMAL GYNECOLOGIC BLEEDING (NONMALIGNANT)

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THE various drug remedies employed, heretofore in the treatment of benign gynecologic bleeding have been largely disappointing, due, perhaps, to improper selection and use of some, and the prohibitive cost of others. In search of such a remedy, therefore, as would yield uniformly satisfactory results and have at the same time an economic appeal, we were impressed favorably with the published results of Karnaky¹ from the use of stilbestrol in oil and undertook the following study.

Cognizant, however, of the criticisms and many questions concerning the pharmacodynamics, for which we had not the answer, and mindful of the possible recriminations aroused by use of this paradoxically acting and potentially carcinogenic drug, we continued its use with satisfaction, as the bleeding was being controlled with unfailing suddenness where other drugs had failed. The progression of anemia was arrested and the woman, relieved of anxiety, returned to her home with the feeling that something had been done for her.

Explanation of the mechanism of stilbestrol, according to Karnaky, is as follows: "At a certain estrogenic hormonal blood level which varies in each individual and locality, a constriction of the spiral arteries of the endometrium occurs. This leads to anemia, dehydration, anoxemia, necrosis, dilatation of the spiral arteries and subsequently to bleeding or menstruation. A woman bleeds or menstruates only when the estrogenic hormones reach a certain blood level, above and below which the woman is amenorrhic regardless of the condition, size, position, shape, or contents of the uterus."¹

The purpose of this paper is to report our experience and findings in controlling uterine bleeding with stilbestrol* in our hospital and out-patient services and to point out certain worth-while observations.

Clinical material for this study was obtained through the cooperation of our indoor and outdoor staffs, many of whom allowed the records of their private patients to be used in order to increase the scope and evaluation of the report. These patients were unselected and presented themselves invariably because of excessive uterine bleeding.

Following a gynecologic history and vaginal examination, biopsy of the endometrium was taken, followed by an injection of stilbestrol (25 mg. per c.c. in oil) into the anterior lip of the uterine cervix. The patient was then allowed to go home and, on the next morning, the following determinations were made: basal metabolic rate, bleeding time, coagulation time, and hemoglobin. If, at

*Acknowledgment with thanks is hereby made to the Winthrop Chemical Company, The Abbott Company and The Burroughs Wellcome Company for supplying the drug material for this study.

ferred with unless there is some extensive organic pelvic pathology requiring surgical treatment. One such patient (No. 2) who was difficult to manage had a history of functional type of bleeding over a period of nineteen years. At operation, extensive unilateral cystic disease of the ovary was found, despite the fact that at operation nine years previously the ovary was reported to be normal.

Our observations and experience, based on the results of this study during the past three years, warrant the conclusion that the use of stilbestrol as described herein is a safe, economic, practicable, and effective therapeutic agent for abnormal gynecologic bleeding (nonmalignant), not only as a temporary expedient, but as a long-range, satisfactory remedy in a significant number of the cases.

Summary

1. In more than 200 cases, excessive gynecologic bleeding (nonmalignant) was controlled satisfactorily in 99 per cent by the injection of stilbestrol in oil (25 mg. per c.c. dosage) into the anterior lip of the cervix uteri.

2. A critical analysis of 60 cases revealed that 58.3 per cent ranged from 20 to 30 years of age; 70 per cent had decreased thyroid function; 70 per cent had pelvic disorders; 71.4 per cent were menorrhagic and menometrorrhagic; 70.2 per cent bled from a proliferative endometrium and infertility was significantly higher.

3. Large or repeated dosage of stilbestrol did not cause toxic symptoms of sufficient intensity to warrant its discontinuance or modification.

4. The pelvic disorders did not contraindicate such use of stilbestrol.

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TABLE III. TYPES OF BLEEDING

| AGE GROUPS | 10-20 | 20-30 | 30-40 | 40-50 | TOTAL | PER CENT |
|------------------|-------|-------|-------|-------|-------|----------|
| Menorrhagia | 2 | 19 | 6 | | 26 | 41.2 |
| Metrostaxis | 1 | 14 | 3 | | 18 | 28.6 |
| Menometrorrhagia | 3 | 8 | 6 | 2 | 19 | 30.2 |

specimens (22.6 per cent) revealed the endometrium to be in a poorly differentiative phase. This was true when a correction was applied for twelve reports revealing three submucous leiomyomas, four retained secundines, and five specimens marked unsatisfactory for study. It is interesting that the bleeding was controlled equally as well in these latter cases as in the others. These results became more significant when the age groups were broken down showing that 35 (58.3 per cent) ranged from 20 to 30; 15 (25 per cent) 30 to 40; 8 (13.3 per cent) 10 to 20; 2 (3.3 per cent) over 40.

TABLE IV. ENDOMETRIAL BIOPSY

| | AGE GROUP | | | | TOTAL | PER CENT |
|-------------------------|-----------|-------|-------|-------|-------|----------|
| | 10-20 | 20-30 | 30-40 | 40-50 | | |
| Proliferative phase | 6 | 21 | 10 | | 37 | 70.7 |
| Differentiative phase | | 10 | 2 | | 12 | 22.6 |
| Hyperplasia | 1 | | 1 | | 2 | 3.6 |
| Endometritis | | 1 | 1 | | 2 | 3.6 |
| Submucous fibroid | | 1 | 1 | 1 | 3 | |
| Retained secundines | | 4 | | | 4 | |
| Specimen unsatisfactory | | 1 | 3 | 1 | 5 | |

TABLE V. AGE DISTRIBUTION

| AGE | NO. | PER CENT |
|-------|-----|----------|
| 10-20 | 8 | 13.3 |
| 20-30 | 35 | 58.3 |
| 30-40 | 15 | 25.0 |
| 40-50 | 2 | 3.3 |

Although the majority of these women were in the childbearing period, these bleeding disorders predated relative barrenness, since 67 pregnancies, a small number for the number of women in this age group, resulted in but 62 childbirths. This is particularly noteworthy since only ten women (16.6 per cent) were in the age groups where pregnancy is undesirable (10-20 years and over 40).

Vaginal examinations revealed that 70 per cent had some type of pelvic disorder evidenced by infection, adnexal masses or tenderness, bleeding fibroids, malpositions of the uterus and its adnexae. Apparently, neither was the effectiveness of the treatment reduced by these disorders nor the amount and frequency of administration of the drug altered thereby.

All of the cases had various phases of anemia but no abnormalities were noted in the bleeding or clotting time of a single case nor evidence of avitaminosis. Hence, no vitamin or liver deficiency studies were made.

In view of the fact that in 70.7 per cent the endometrium was in the proliferative phase, that 70.4 per cent of the bleeding occurred at the normal menstrual period, that the majority of these women had evidence of hypothyroid function, the study indicated that, probably, abnormal ovarian functioning was responsible directly or indirectly for the bleedings.

Furthermore, studies on the follow-up patients are in agreement with the results of others, in that the return of the normal menstrual cycle is not inter-

ago, when remarkable results were published in an official medical journal and later exploited in the sensational daily press. Many critical readers believed this report to be unduly roseate and certain claims seemed incongruous with vital statistics.

In response, therefore, to the informal suggestions of a few associates on the National Committee of Maternal Health, your reporter agreed, in 1939, to investigate the biological and psychological results which might be obtained by semi-adoption providing the following ideals could be realized:

1. The husband and wife were to be interviewed and the infertility and cooperation of the husband confirmed. Furthermore, signatures granting permission for the procedure were to be obtained after the uncertainties and limitations of the method were fully explained.
2. Only donors with a normal degree of fertility and with a cultural and eugenic background equal or superior to that of the patients were to be used. Broad racial and religious prejudices were to be satisfied, and, more recently, the Rh factor, when known, was given consideration.
3. Specimens were to be prepared at the office or delivered promptly from a short distance, thus aiming to avoid any unknown changes that might result from aging or artificial preservation of the semen.
4. Adequate examinations giving reasonable assurance of the wife's fertility were to be made and insemination deferred pending the correction of poor health, hypothyroidism, habitual menstrual irregularities, or other inhibitory factors.
5. Patients were to be accorded complete privacy and were to cooperate with plans to assure no possible meeting or identification between donor and patient. This was accomplished by having patients contact the office from a near-by telephone for instructions ten minutes before their appointment.
6. Patients with little hope of successful issue or those planning to supply their own donor were to be promptly discouraged.

The results seem to have justified this onerous but precautionary program.

Biologic Results

In a period of approximately seven years, 83 couples, in whom the wife was appraised as potentially fertile, applied for artificial insemination on 89 occasions, with successful results in 66 cases. Pregnancy followed the first insemination in 21 instances. In order to avoid the basic criticism directed toward some previous statistics and to provide a complete clinical picture, it should be stated that seven pregnancies terminated as miscarriages and there was one mole and one ectopic gestation. In the opinion of the writer, these complications were not at variance with normal expectations. A new donor had been used in the case of placental degeneration and, because of a personal bias rather than any scientific conviction, this specimen was not employed again. It is possible the ectopic might have been avoided had the physician's advice prevailed. This talented and determined wife gave a previous history of many unsuccessful trials of artificial insemination. The adolescent and mature records were not explanatory but the uterus was sensitive and in advanced retroversion. Reposition and pessary support were ultimately accomplished and a favorable uterine secretion was demonstrated concomitant with the estimated period of high follicular activity. Immediate success and an uneventful delivery followed the first insemination. This enthusiastic patient returned a few months later with a postpartum

RESULTS OF ARTIFICIAL INSEMINATION WITH AN EXTRAMARITAL SPECIMEN (SEMI-ADOPTION)

Report on 89 Cases

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DURING a period of seven years, 83 couples, in whom the wife was appraised as potentially fertile, have applied for semi-adoption on 89 occasions with 66, or 74 per cent, successful results. Fertilization at the first insemination occurred in 21 cases. The immediate psychological reactions were generally gratifying but the ultimate or teleologic results belong to the future.

An itemized list of the successful cases is submitted, showing the menstrual pattern in each case, the day of fruitful insemination, and, in most cases, an accurate record of the carrying time. Certain unique cases are briefly abstracted.

The eugenic, ethical, and biologic ideals which the writer believes essential to this work are presented. No dogmatism is intended, as it is assumed each individual will be governed by his own philosophy. Irresponsible practices may eventually and properly lead to legal restrictions.

The various observations which may guide the attendant in selecting the most favorable day for insemination are discussed in some detail. In computing the day of cycle the writer counts the day after onset of menstruation as one elapsed day.

No immediate or deferred pelvic reaction is known to have occurred in this series. This is attributed to great care in avoiding invasion of the internal os by instrument or seminal specimen.

Because the public has embraced a more intelligent and realistic philosophy concerning sex and eugenics and because greater, and possibly unwarranted, restrictions are imposed upon those seeking desirable offspring for regular adoption, an increasing number of childless couples are consulting physicians regarding the feasibility of fertilizing the wife with an extramarital semen, a procedure which the writer has designated as semi-adoption.

The method has no justification, of course, except in those marriages in which the infertility of the husband is incurable and the innate and compelling urge of the wife to experience reproduction is honored by the mate. Opposition may be based upon the interpretation of ancient, ecclesiastic dogmas or the idea may be opposed in principle by some physicians and their patients. One readily agrees that such considered opinions should be respected but it would seem that couples whose religious, ethical, and social convictions have led to a favorable decision should have access to sympathetic guidance and to responsible care in suitable cases. Artificial fertilization of the female has a relatively long history in husbandry and medicine, but interest in the use of an alien semen for the relief of certain barren marriages was again stimulated approximately a decade

Supplementary Statistics

An itemized list of 66 successful cases is presented to show the predominate menstrual cycle, the day on which the fruitful insemination was performed, and the actual number of days which elapsed until delivery. It was believe this last item might be of interest to obstetricians. These data were accumulated by restricting insemination to a single trial in each cycle. Exceptions were made for a few patients who came from very distant points and, therefore, elected two or three trials during a single cycle. The "carrying time" is necessarily omitted in such instances and in a very few additional cases in which the date of delivery was not reported.

In our early experience, it was noted that menstruation of normal patients was sometimes delayed for many days following the initial insemination, which led to false hope and proportionately severe disappointment. One of these patients, a keen psychologist, confirmed our impression that this delay was caused by mounting anxiety as the time of the next period approached; and she suggested that this tension might be relieved if the original contract provided, when necessary, for insemination during three separate cycles and thus gave greater assurance of ultimate success. This plan improved the morale of patients and possibly contributed to the effectiveness of the procedure.

Day of Successful Insemination

For two decades prior to the inception of this study and for some years before the time of human ovulation was generally established, the writer had been studying the cervical secretion in various phases of the menstrual cycle to determine the most favorable time to conduct the postcoital test. In 1930, we published an analysis of 200 postcoital studies and noted that there was an ideal time, a few days after the cessation of the period, when the canal of the healthy cervix was distended with a clear, glistening, less viscid mucus which overflowed from the gaping external os into the vaginal vault. This condition, which was called the weeping cervix, evidently favored spermatozoal invasion. It was not, however, until distinguished experimenters had clarified the physiology of ovulation and coordinated it with the menstrual cycle that we recognized the weeping cervix as a manifestation of high follicular activity and impending ovulation. By the experience gained in correlating the time of this phenomenon with the length of the cycle, it was often possible, after reviewing the menstrual pattern of the prospective patient, to predict the most propitious time for insemination with fair accuracy. In other so-called regular patients, there was sufficient variability in the cycle to introduce an element of chance. It is significant that typical hypersecretion of the cervix was present at the time of insemination in every case in which conception followed the first insemination.

In reviewing the cases, it appears that the fruitful inseminations were performed one or two days earlier than the generally accepted time of ovulation. The same observation was reported by Rock in a personal communication. In this series, for instance, 56 pregnancies could be definitely credited to a single insemination per cycle and, of these, 17 were recorded on the eleventh and 13 on the twelfth day of the cycle. These two days, therefore, account for nearly one-half of the total conceptions and for approximately 70 per cent of the pregnancies occurring in women who menstruated every 27 to 29 days. Four fertilizations were secured on each of days 13 and 15 of the cycle and five on the fourteenth day, the latter days being selected for patients who flowed every 30 to 32 days. One patient with a cycle of 34 days responded on the sixteenth day. Insemination proved effective on the tenth day on 10 occasions and included many patients with

retroversion and some signs of incomplete involution. The displacement was readily supported and she refused to defer insemination pending more complete involution. The first trial was again successful but terminated in a salpingo-oophorectomy for tubal pregnancy. Without critical comment and ignoring a doubtful prognosis, she requested insemination the following year and was successfully delivered.

Psychological Results

The psychological results must be estimated by the reaction of couples with varying temperaments and articulative abilities. The ultimate or teleologic results belong to the future and are as unpredictable as human destiny. The contemporary reactions of these patients seem to have been universally gratifying and, in several instances, the husband made a special effort to register his appreciation. Temporary anxiety was exhibited by one wife delivered more than two weeks after the estimated date of confinement. She and her husband had practiced contraception simultaneously for years (condom and vaginal diaphragm) to avoid reproduction, because a serious physical deformity had occurred in every traceable generation of the husband's family. She feared that the late delivery might indicate failure of contraception rather than successful insemination.

Failures and Deferred Successes

Each couple was informed at the outset that obscure and variable factors were involved and they must anticipate the possibility of failure. Experience has seemed to demonstrate that a less favorable prognosis should be entertained when three or four inseminations, conducted under favorable indications, have failed. Under the latter circumstances, a few patients applied for full adoption, while many others accepted failure stoically and apparently found satisfaction in having made every practicable effort. Only four couples elected to plan for more than eight trials, and three ultimately terminated successfully on the ninth, twelfth, and twenty-first inseminations, respectively.

The first of this triad was a small, asthenic, and cultured girl with low blood pressure, a metabolism of minus twelve, and a cervical stenosis which evidently followed an earlier cauterization for erosion and discharge. After six trials, the attending gynecologist, in another city, cooperated by performing a premenstrual dilation and light curettage. A mature, secretory endometrium was reported. Thyroid therapy was resumed and, after several weeks, two inseminations in one cycle proved efficient. After an early threat of miscarriage she was successfully delivered. The second patient was a thin, tense, but apparently healthy girl who menstruated every 24, 25, or, less frequently, every 26 days and presented no anatomic or metabolic disturbances. In our general, clinical study of female sterility, we have found that patients of this type belong to a low-fertility group; and, from an extensive experience in the study of vaginal smears, Papanicolaou asserts that women with habitual cycles of every 24 days or less rarely ovulate normally. The third patient was meticulously investigated in office, laboratory, and finally, at her request, under anesthesia at the hospital without revealing any inhibitory factor. The endometrium reflected full follicular evolution but smears were less decisive. In each of these cases, success was finally attained on a day of the cycle and with a specimen that had been repeatedly used without result.

At least nine failures resulted when patients insisted upon the undertaking although disadvantageous factors were present and a less favorable prognosis was given. Experience suggests that minor disorders of the pelvis and lesser seminal defects which would not prevent conception indefinitely under marital conditions assume major significance in artificial impregnation.

cycles of 26 to 28 days. One patient with a cycle of 24 to 26 days responded on the ninth and one on the eighth day; and two patients with habitual cycles of 24 days terminated as failures.

Temperature Graphs and Endometrial Biopsies

In 1940, following a visit to Zuck's clinic, the writer experimented with temperature graphs as a supplementary measure for revealing the favorable time for artificial insemination. The procedure was found impracticable and was abandoned, except in occasional obscure cases, for the following reasons:

- a. Some patients submitted carelessly arranged lists of dates and temperatures which they expected the office to chart and interpret.
- b. Many graphs were equivocal in type or vital notations were modified or omitted because of minor illness, travel, or other complications.
- c. Typical graphs varied from cycle to cycle in the same patient and the triangular appointment at the office was necessarily made some days before the contemporary graph could be known.

Three patients conceived while experimental graphs were being compiled and, although the material is meager, it was noted that insemination coincided with the day of lowest temperature in two, and was done the following morning in one patient whose previous graphs were atypical. Several articles relative to basal temperatures have been published since 1945, notably that of Tompkins. A correlated study of basal temperatures and endometrial biopsies by Buxton will appear later.

An endometrial biopsy has not been regarded as an essential step in qualifying the wife for a trial of semi-adoption. The writer has long held that evidence of follicular evolution in the ovary gives no assurance that the ovum is intrinsically fecund or that normal implantation of the ovum will be effected. This clinical opinion was based upon many years' experience, during which correlated diagnostic studies of both partners were conducted routinely by the writer. The clinical data supporting this inference will not be detailed again because direct confirmation has been submitted recently by the unique and instructive investigations of Hertig, who assembled, over a period of years, twenty-four uteri in which implantation of the ovum had just occurred. By means of sections through ovum and endometrium he demonstrated ten instances in which an abnormal ovum was associated with a normal secretory endometrium. In four cases, the attachment was so precarious that sloughing and degeneration could be anticipated before menstruation was due. Furthermore, in studying the far more numerous cases of conventional sterility, the writer has found that premenstrual biopsies and curettings from normally menstruating women have been reported, with rare exception, as normally secretory in type. Highly irregular or scanty periods are rarely encountered in the relatively small group of patients seeking semi-adoption because a poor prognosis is anticipated by them.

References

- Zuck, T. T.: AM. J. OBST. & GYNEC. 36: 998, 1938.
Hertig, A. T.: Conference on Sterility, 1947, Charles C Thomas. (In press.)

TABLE I. ITEMIZED LIST OF PREGNANCIES

| NO. | AGE | TYPE OF CYCLE | DAY OF INJECTION | DAYS IN UTERO |
|-----|-----|------------------|---------------------|------------------|
| 1 | 25 | 33-35 | 16 | 278 |
| 2 | 25 | 26 | 11 | |
| 3 | 34 | 25-29 | 9-11-12 | |
| 4 | 34 | 27-29 | 12 | 269 |
| 5 | 34 | 28-30 | 15 | 261 |
| 6 | 25 | 27-32 | 14 | 271 |
| 7 | 23 | 27-28 | 12 | |
| 8 | 36 | 28-30 | 12 | 282 |
| 9 | 23 | 28 | 2d week | |
| 10 | 31 | 28 | 11-12 | |
| 11 | 30 | 30 | 12 | 278 |
| 12 | 26 | 31-34 | 16-17 | |
| 13 | 27 | 28 | 13 | 263 |
| 14 | 26 | 28-33 | 11 | 277 |
| 15 | 23 | 33-35 | 15 | 262 |
| 16 | 30 | 28-30 | 12 | |
| 17 | 37 | 28 | 11 | |
| 18 | 30 | 26-27 | 11 | 259 |
| 19 | 32 | 23-26 | 10 | |
| 20 | 27 | 26-29 | 11 | |
| 21 | 36 | 27-36 | 14 miscarriage | |
| 22 | 28 | 28 | 15 miscarriage | |
| 23 | 27 | 27-30 | 12 miscarriage | |
| 24 | 30 | 29 | 12 | 279 |
| 25 | 34 | 28 | 10 | 272 |
| 26 | 30 | 27-30 | 11 | 266 |
| 27 | 38 | 28 | 11 miscarriage | |
| 28 | 27 | 25-27 | 10-12 | |
| 29 | 29 | 28 | 12 | 274 |
| 30 | 24 | 27-30 | 11 | |
| 31 | 28 | 26-27 | 10 | 269 |
| 32 | 34 | 28 | 11 | |
| 33 | 30 | 24-26 | 9 | 273 |
| 34 | 21 | 30 | 14 | 273 |
| 35 | 34 | 24-26 | 8 | 224 twins |
| 36 | 27 | 30-31 | 13-15 | |
| 37 | 34 | 27-29 | 11 | |
| 38 | 36 | 26-27 | 13 | 261 |
| 39 | 22 | 32-34 | 12 | 255 |
| 40 | 28 | 26 | 11 | 281 |
| 41 | 37 | 26-29 | 13 miscarriage | |
| 42 | 24 | 33 | 12 miscarriage | |
| 43 | 34 | 26-28 | 11 | |
| 44 | 33 | 25-27 | 10 | 282 |
| 45 | 26 | 30 | 13 | 295 |
| 46 | 25 | 28-29 | 11 | |
| 47 | 33 | 30-32 | 12 | |
| 48 | 38 | 24-27 | 11 | 274 |
| 49 | 28 | 26-27 | 11 | |
| 50 | 24 | 26-30 | 10-13 miscarriage | |
| 51 | 24 | 30-42 | 16-19 | |
| 52 | 34 | 24-28 | 10 | 268 |
| 53 | 25 | 30 | 14 | |
| 54 | 40 | 28-30 | 12 | 282 |
| 55 | 28 | 28-33 | 11-13 | |
| 56 | 26 | 33-35 | 15 | 265 |
| 57 | 35 | 24-27 | 10 | 266 |
| 58 | 28 | 25-31 | 11 | 267 |
| 59 | 31 | 28-30 | 11 | 273 |
| 60 | 37 | 25-29 | 10 | 268 |
| 61 | 30 | 30-31 | 14 mole | |
| 62 | 29 | 26-27 | 10 | 272 |
| 63 | 31 | 26-27 | 10 ectopic | |
| 64 | 28 | 30-31 | 13-15 | |
| 65 | 24 | 33 | 12 | 272 |
| 66 | 32 | 26-27 | 10 | 267 |

4. *Severe dysmenorrhea*—patient had severe enough abdominal pain to require her to lose time from work, lose time from her household duties, or require her to go to bed.

Nausea and vomiting of pregnancy was likewise placed in four groups:

1. No nausea nor vomiting—this meant that the patient did not even have morning nausea once.

2. Mild nausea or vomiting—patient had nausea or vomiting which did not persist beyond the first three months.

3. Moderate nausea or vomiting—patient had nausea or vomiting for the entire pregnancy, but not severe enough to require treatment or hospitalization.

4. Severe nausea or vomiting—patient had nausea or vomiting severe enough to require active therapy by injection of vitamins or hospitalization.

No cases of toxemia were included in this series; that is, true toxemia with elevated blood pressure, edema, and albuminuria.

Any classification for gradation of either of the symptom complexes is difficult and probably inadequate because of the difference in pain threshold of different patients, but I tried to minimize this by careful questioning, and, according to Miller,² a patient has pain if she thinks she does.

As will be seen from the tables, using the four stages for each of the two symptom complexes, there are sixteen possible combinations.

TABLE I

| GRAVIDA | GROUPS | | | | | | | | | | | | | | | | TOTAL |
|---------|--------|-----|----|---|----|-----|----|---|----|-----|----|----|----|----|----|----|-------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | |
| i | 57 | 36 | 4 | 0 | 33 | 164 | 6 | 3 | 21 | 67 | 14 | 4 | 10 | 21 | 7 | 4 | 451 |
| ii | 61 | 41 | 4 | 2 | 23 | 99 | 8 | 1 | 6 | 29 | 13 | 5 | 0 | 6 | 0 | 4 | 302 |
| iii | 20 | 18 | 1 | 0 | 9 | 38 | 6 | 0 | 2 | 11 | 8 | 1 | 1 | 3 | 1 | 2 | 121 |
| iv | 17 | 11 | 1 | 0 | 1 | 16 | 1 | 0 | 1 | 8 | 2 | 0 | 0 | 0 | 0 | 2 | 60 |
| v | 7 | 3 | 2 | 0 | 4 | 11 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 32 |
| vi | 5 | 1 | 0 | 0 | 0 | 6 | 1 | 0 | 0 | 4 | 0 | 1 | 1 | 0 | 0 | 0 | 19 |
| vii | 1 | 1 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 10 |
| viii | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| ix | 1 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 5 |
| x | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 6 |
| Total | 169 | 113 | 12 | 2 | 70 | 344 | 23 | 5 | 30 | 122 | 42 | 12 | 12 | 30 | 8 | 14 | 1008 |

- Group 1 No dysmenorrhea and no nausea nor vomiting.
- Group 2 No dysmenorrhea and mild nausea or vomiting.
- Group 3 No dysmenorrhea and moderate nausea or vomiting.
- Group 4 No dysmenorrhea and severe nausea or vomiting.
- Group 5 Mild dysmenorrhea and no nausea nor vomiting.
- Group 6 Mild dysmenorrhea and mild nausea or vomiting.
- Group 7 Mild dysmenorrhea and moderate nausea or vomiting.
- Group 8 Mild dysmenorrhea and severe nausea or vomiting.
- Group 9 Moderate dysmenorrhea and no nausea or vomiting.
- Group 10 Moderate dysmenorrhea and mild nausea or vomiting.
- Group 11 Moderate dysmenorrhea and moderate nausea or vomiting.
- Group 12 Moderate dysmenorrhea and severe nausea or vomiting.
- Group 13 Severe dysmenorrhea and no nausea or vomiting.
- Group 14 Severe dysmenorrhea and mild nausea or vomiting.
- Group 15 Severe dysmenorrhea and moderate nausea or vomiting.
- Group 16 Severe dysmenorrhea and severe nausea or vomiting.

Of the total of 1,008 patients, there were 451 primigravidas (44 per cent) and 557 (56 per cent) multigravidas. Of the multigravidas, the largest group was the gravidas ii and iii, these comprising 423 cases (76 per cent) of the multigravidas or 41 per cent of the total. The cases were broken down into

SOME PSYCHIC ASPECTS OF DYSMENORRHEA AND NAUSEA AND VOMITING OF PREGNANCY

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THERE have been many reasons given for dysmenorrhea, and as many for nausea and vomiting of pregnancy. Many forms of therapy have been tried for each. Obviously, any disease or symptom complex for which so many forms of treatment are advocated leads to one of three conclusions: first, there are many causes and thus no cure-all; second, the correct cause has not been found, therefore no correct treatment; or third, the basis is psychic. The treatment of the symptoms is still a very urgent problem for the doctor and to the patient, but of all the methods in use today none have proved entirely successful, even though some patients have obtained relief from some of the methods. Was it, however, the particular method or would any one of the many of them have done the same thing?

The cause of dysmenorrhea is unknown, but many theories have been advanced. Among the latter we find cervical stenosis, myometrial insufficiency, mucosal faults, vascular faults, ovarian causes, thyroid causes, anterior hypophyseal causes, allergic phenomena, uterine displacements, psychic and nervous factors. Many of the characteristics of the symptom have led eminent workers to advance a psychogenic basis as the cause.

The symptom complex of nausea and vomiting of pregnancy, like dysmenorrhea, is of unknown etiology, although many theories have been advanced, among them the neurogenic and the psychogenic. Again, as with dysmenorrhea, many therapies have been tried, ranging all the way from sterile hypodermics with a dull needle to hypnosis, forced hydration, and proctoclysis with the patient's own urine, but no one form of treatment has been uniformly successful.

Noting all the emphasis placed on the psychic factors in both dysmenorrhea and also nausea and vomiting of pregnancy, I wondered if the severity of these two symptom complexes ran a parallel course, which might be suggested by the work of Smith and Smith,¹ since they place the two on a common etiologic basis. With this in mind, I interviewed every patient admitted to the obstetric wards of Watts Hospital during the period Jan. 15, 1946, to May 15, 1947, and questioned her as to the severity of her dysmenorrhea and also her nausea and vomiting.

Dysmenorrhea was placed in four groups with the following as the basis for the classification:

1. *No dysmenorrhea*—patient was not aware of menstruation, except for the flow.
2. *Mild dysmenorrhea*—patient had abdominal discomfort, but not severe enough to require any analgesic.
3. *Moderate dysmenorrhea*—patient usually took an analgesic, although sometimes it was only an aspirin.

parentheses with the total number of actual cases in each instance, for the total number of cases for the other groups are closely parallel:

1. No dysmenorrhea and no nausea or vomiting—a total of 169 cases, while on the basis of chance alone there should be only 82.
2. Mild nausea or vomiting and mild dysmenorrhea—a total of 344 cases, while on the basis of chance alone there should be 266.
3. Moderate dysmenorrhea and moderate nausea or vomiting—a total of 42 cases, while chance provides for only 17.
4. Severe dysmenorrhea and severe nausea or vomiting—a total of 14 cases, where there should have been only 2 on a chance basis.

Adding the total number of actual cases, we have 569, while by chance alone we should have had only 367, a difference of 202 cases. This is 55 per cent more than would be expected on the basis of chance alone. In the primigravidas, this difference amounted to 44 per cent, in the gravidas ii and iii to 57 per cent, and in the gravidas iv and above to 88 per cent. Thus the gravidas ii and iii came nearer to the standard for the group as a whole, while the gravidas iv and above showed the most marked difference. The latter might possibly be accounted for on the basis of a greater number of repeated insults.

TABLE II. ALL CASES

| | DYSMENORRHEA | | | | TOTAL |
|-----------------------------|--------------|-----------|-----------|---------|-------|
| | NONE | MILD | MODERATE | SEVERE | |
| No nausea or vomiting | 169 (82) | 70 (123) | 30 (57) | 12 (18) | 281 |
| Mild nausea or vomiting | 113 (178) | 344 (266) | 122 (124) | 30 (38) | 609 |
| Moderate nausea or vomiting | 12 (25) | 23 (37) | 42 (17) | 8 (5) | 85 |
| Severe nausea or vomiting | 2 (9) | 5 (14) | 12 (6) | 14 (2) | 33 |
| Total | 296 | 442 | 206 | 64 | 1008 |

TABLE III. PRIMIGRAVIDAS

| | DYSMENORRHEA | | | | TOTAL |
|-----------------------------|--------------|-----------|----------|---------|-------|
| | NONE | MILD | MODERATE | SEVERE | |
| No nausea or vomiting | 57 (26) | 33 (55) | 21 (28) | 10 (11) | 121 |
| Mild nausea or vomiting | 36 (62) | 164 (131) | 67 (67) | 21 (26) | 288 |
| Moderate nausea or vomiting | 4 (7) | 6 (14) | 14 (7) | 7 (3) | 31 |
| Severe nausea or vomiting | 0 (2) | 3 (5) | 4 (2) | 4 (1) | 11 |
| Total | 97 | 206 | 106 | 42 | 451 |

TABLE IV. GRAVIDAS II AND III

| | DYSMENORRHEA | | | | TOTAL |
|-----------------------------|--------------|-----------|----------|--------|-------|
| | NONE | MILD | MODERATE | SEVERE | |
| No nausea or vomiting | 81 (42) | 32 (53) | 8 (21) | 1 (4) | 122 |
| Mild nausea or vomiting | 59 (84) | 137 (106) | 40 (43) | 9 (9) | 245 |
| Moderate nausea or vomiting | 5 (14) | 14 (17) | 21 (7) | 1 (1) | 41 |
| Severe nausea or vomiting | 2 (5) | 1 (6) | 6 (3) | 6 (1) | 15 |
| Total | 147 | 184 | 75 | 17 | 423 |

TABLE V. GRAVIDAS IV AND OVER

| | DYSMENORRHEA | | | | TOTAL |
|-----------------------------|--------------|---------|----------|---------|-------|
| | NONE | MILD | MODERATE | SEVERE | |
| No nausea or vomiting | 31 (14) | 5 (14) | 1 (7) | 1 (1) | 38 |
| Mild nausea or vomiting | 18 (29) | 43 (29) | 15 (14) | 0 (2) | 76 |
| Moderate nausea or vomiting | 3 (5) | 3 (5) | 7 (2) | 0 (0.4) | 13 |
| Severe nausea or vomiting | 0 (2) | 1 (2) | 2 (1) | 4 (0.2) | 7 |
| Total | 52 | 52 | 25 | 5 | 134 |

three groups because it was felt that psychologically the primigravidas were different from the others. It was also felt that the gravidas ii and iii were different from those above gravida iii, the distinction being that in most instances the gravida i planned on the first baby, the gravidas ii and iii wanted the baby, and beyond gravida iii, in most cases, the woman didn't know what to do about keeping from having more children or didn't do it.

Those groups containing the largest number of cases were:

1. Mild dysmenorrhea and mild nausea and vomiting—344 cases (34.1 per cent)
2. No dysmenorrhea and no nausea nor vomiting—169 cases (16.7 per cent)
3. Moderate dysmenorrhea and mild nausea and vomiting—122 cases (12.1 per cent)
4. No dysmenorrhea and mild nausea or vomiting—113 cases (11.2 per cent)
5. Mild dysmenorrhea and no nausea nor vomiting—70 cases (6.9 per cent)
6. Moderate dysmenorrhea and moderate nausea or vomiting—42 cases (4.1 per cent)

The four groups that were considered similar were:

1. No dysmenorrhea and no nausea nor vomiting—169 cases (16.7 per cent)
2. Mild dysmenorrhea and mild nausea or vomiting—344 cases (34.1 per cent)
3. Moderate dysmenorrhea and moderate nausea or vomiting—42 cases (4.1 per cent)
4. Severe dysmenorrhea and severe nausea or vomiting—14 cases (1.4 per cent)

If one adds the cases contained in the above four groups we will find that, of the total of 1008 cases, there were 569, or 56.4 per cent, that had absolutely parallel symptoms. If we add to that total the group that had moderate dysmenorrhea and mild nausea or vomiting, 112 cases, for in a great many instances only an aspirin was used to relieve the pain, we obtain a total of 691 cases, or 68.5 per cent of the total, which had parallel courses.

Some of the other groups should be noted. There were only two cases of severe nausea and vomiting in those who had no dysmenorrhea. It will also be noted that there were only five cases of mild dysmenorrhea who had severe nausea or vomiting.

A total of 296 cases had no dysmenorrhea (29.6 per cent). There were 442 cases (43.8 per cent) of mild dysmenorrhea, 206 cases (20.4 per cent) of moderate dysmenorrhea, and 64 cases (6.3 per cent) of severe dysmenorrhea.

There was no nausea nor vomiting in 281 cases (27.8 per cent), mild in 609 cases (60.4 per cent), moderate in only 85 cases (8.4 per cent) and 33 cases (3.2 per cent) had severe nausea or vomiting. Thus there were 70.5 per cent of all the women in the series who had dysmenorrhea of some degree and 72.1 per cent with nausea or vomiting during pregnancy.

It might be contended that, since there were only 56.4 per cent of the cases that had exactly parallel courses, that figure might be obtained on the basis of chance alone. The total number of cases in each group are not in parentheses while the number that would be expected in that group on the basis of chance alone are included in the parenthesis. It will be seen from a comparison of the figures that in only a few instances are they very close together, as might be expected if the distribution of my cases took place on the chance basis. In a table of the type I have set up, the distribution should run from the upper left-hand corner to the lower right-hand corner. Let us compare the figures in the

BACTERIAL FLORA IN INFANTS ENCOUNTERED AT TIME OF DELIVERY*

A Study of One Hundred Cultures from the Eyelids

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THE obstetrician is concerned with the bacterial flora contaminating the operative field at the time of the delivery of an infant. Both he and the pediatrician are interested in the incidence and types of organisms from the mother which might cause ophthalmia neonatorum in the newborn infant. As a method of demonstrating this bacterial flora, one hundred cultures were taken from the eyelids of newborn infants immediately after birth, before the umbilical cord was cut.

Mothers of Infants Studied

Nearly all of the mothers were charity patients. Seventy-nine per cent belonged to the Negro race. They were unselected, except that no patient was included who had not been completely draped and prepared for delivery in the usual manner.

In order to evaluate the incidence of venereal disease in this group, the Kahn test of the mother at the time of the first prenatal visit was noted, and the mother was questioned at the time of delivery regarding a vaginal discharge occurring prior to the present pregnancy and whether or not she had received treatment for it. She was also questioned about having received therapy for syphilis.

The Kahn test was known in 77 patients and was positive in 5 (6.5 per cent). Twelve (14.4 per cent) out of 83 patients (unknown in 17) had received therapy for syphilis. Thirty-eight (40.4 per cent) out of 94 patients (unreliable history in 6) gave a history of a vaginal discharge, and 13 (13.6 per cent) had received treatment for it.

Eighty-nine per cent of the patients had not had a vaginal examination during labor; 9 per cent had had one, and 2 per cent had had two vaginal examinations. The membranes had been ruptured less than twelve hours in 83 per cent.

Collection of Specimens for Culture

The cultures were taken before the umbilical cord of the infant was cut, to rule out any possible contamination other than from the mother. A sterile swab was wiped across the eyelids along the line of approximation of the eyelid margins. The eyes were closed at the time. This was done on

*Submitted to the Department of Obstetrics and Gynecology of the University of Tennessee in partial fulfillment of the requirements for the degree of Master of Science in Obstetrics and Gynecology.

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In conclusion, my correlation shows that there is some common factor between dysmenorrhea and nausea and vomiting which could be psychogenic and the statistics cause one to have grave suspicion that such may be the case, since there is no obvious anatomic or physiologic relationship known.

Summary

1. One thousand and eight patients were interviewed with regard to dysmenorrhea and nausea and vomiting of pregnancy.
2. There was no dysmenorrhea in 296 cases (29.6 per cent).
3. There was no nausea nor vomiting in 281 cases (27.8 per cent).
4. There were 569 cases (56.4 per cent) that had absolutely parallel symptoms, and to this might be added another 122 cases, making the total 691 cases (68.5 per cent).
5. A review of the number of cases obtained in each group in comparison with the number that would be expected on a chance basis alone leads one to the conclusion that there is some common factor between dysmenorrhea and nausea and vomiting of pregnancy that could very well be psychogenic, since there is no obvious common anatomic nor physiologic relationship known.

The author expresses his appreciation to Dr. Eleanor B. Easley for her helpful criticisms and suggestions during the preparation of this article.

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TABLE I. TYPE AND INCIDENCE OF ORGANISMS FOUND IN POSITIVE CULTURES FROM EYELIDS OF NEWBORNS IMMEDIATELY AFTER BIRTH

| ORGANISM | INCIDENCE | PER CENT OF TOTAL | |
|--|-----------|-------------------|------|
| <i>Staphylococcus aureus</i> | | | |
| *hemolytic, plasma, coagulase negative | 10 | | |
| *hemolytic, facultative aerobe, plasma coagulase negative | 1 | | |
| nonhemolytic, plasma, coagulase negative | 9 | 50 | 29.9 |
| nonhemolytic, facultative anaerobe, plasma coagulase negative | 1 | | |
| <i>Staphylococcus albus</i> | | | |
| hemolytic, plasma, coagulase negative | 9 | | |
| nonhemolytic, plasma, coagulase negative | 19 | | |
| <i>Staphylococcus, unclassified</i> | 1 | | |
| <i>Escherichia coli</i> | 40 | 24.0 | |
| <i>Streptococcus</i> | | | |
| alpha hemolytic | 1 | | |
| alpha-hemolytic, anaerobic | 7 | | |
| *beta-hemolytic | 2 | | |
| *beta-hemolytic, anaerobic | 6 | | |
| *beta-hemolytic, facultative anaerobe | 4 | 36 | 21.6 |
| nonhemolytic | 2 | | |
| nonhemolytic, facultative aerobe | 3 | | |
| nonhemolytic, anaerobic | 8 | | |
| nonhemolytic, facultative anaerobe | 3 | | |
| Gram-positive sporulating bacillus, unclassified | 11 | 6.6 | |
| * <i>Monilia albicans</i> | 8 | 4.8 | |
| * <i>Bacterium aerogenes</i> | 5 | 3.0 | |
| Diphtheroid, unclassified | 5 | 3.0 | |
| Gram-negative sporulating bacillus, anaerobic, unclassified | 3 | 1.8 | |
| <i>Corynebacterium xerose</i> | 2 | 1.2 | |
| <i>Corynebacterium hoffmannii</i> | 1 | 1.6 | |
| *Gram-negative diplococcus, positive oxidase, atypical fermentation reactions for gonococcus | 1 | .6 | |
| Member of Colon-aerogenes group | 1 | .6 | |
| Gram-negative nonsporulating bacillus, unclassified | 1 | .6 | |
| Gram-negative nonsporulating gas-producing bacillus, unclassified | 1 | .6 | |
| Gram-positive coccus, unclassified | 1 | .6 | |
| Gram-positive coccus, anaerobic, unclassified | 1 | .6 | |
| Total | 167 | | |

*Potential pathogens

Of the total organisms isolated, 15.0 per cent were anaerobes and 4.8 per cent were facultative anaerobes making a total of 19.8 per cent showing culture preference for anaerobic conditions (Table II). Facultative aerobes comprised 2.4 per cent of the total.

TABLE II. INCIDENCE OF AEROBIC AND ANAEROBIC ORGANISMS

| AEROBE | | | | ANAEROBE | | | |
|----------|--------------------|-------------|-------------------|----------|-------------------|-------------|-------------------|
| OBLIGATE | | FACULTATIVE | | OBLIGATE | | FACULTATIVE | |
| NUMBER | PER CENT OF TOTAL* | NUMBER | PER CENT OF TOTAL | NUMBER | PER CENT OF TOTAL | NUMBER | PER CENT OF TOTAL |
| 130 | 77.8 | 4 | 2.4 | 25 | 15.0 | 8 | 4.8 |

*Total of 167 organisms isolated in 100 cultures from surface of eyelids immediately after birth.

Table III groups the staphylococci according to hemolysis; 59.2 per cent were nonhemolytic and 40.8 per cent were hemolytic. No staphylococci were found with the ability to coagulate plasma.

each eye and the swabs put in a tube of nutrient broth. Cultures taken at night were kept in a refrigerator for plating the following morning.

Bacteriologic Procedures

The two swabs were streaked across the surfaces of two plates containing McLeod's medium for isolation of the gonococcus, two blood agar plates, and one eosin methylene-blue agar plate. The broth in the specimen tube was then distributed in approximately equal portions into two tubes of blood tryptose broth.

One tube of blood tryptose broth, one blood agar plate, and the eosin methylene-blue agar plate were incubated at 37.5°C. The other tube of blood tryptose broth and the second blood agar plate were sealed in an earthenware jar, using the Varney¹ method for detecting anaerobic organisms and incubated at 37.5° C. The two plates of McLeod's medium were sealed under 10 per cent carbon dioxide tension, using the method of Wadsworth,² and incubated at 37.5° C. The container was a screw top, five-pound coffee jar which possessed an inner top with a rubber ring to aid in sealing.

At the end of twenty-four hours, the two blood agar plates, the eosin methylene-blue agar plate, and the two culture tubes of blood tryptose broth were examined. If negative, they were examined again at the end of forty-eight hours. At the end of forty-eight hours, the two plates of McLeod's medium were carefully examined for colonies of *Neisseriae*. All plates which were negative after forty-eight hours of incubation were discarded. All broths which were negative after forty-eight hours of incubation were retained and re-examined five days after the specimen was collected. At the end of this period, if the broths were still negative, the culture was considered negative. If positive, the broths were streaked on plates and identification of the organism or organisms made.

Organisms were studied as to microscopic appearance and colony formation. Staphylococci were classified as to their pigment formation, and their capacity for hemolyzing blood and coagulating plasma. The bile solubility test was used to differentiate between streptococcus *viridans* and the pneumococcus. Gram-negative rods were grouped as to motility, pigment formation, their ability to form spores, and action on carbohydrates. Gram-positive rods which gave the microscopic appearance of *Corynebacteria* were inoculated to carbohydrate broths to differentiate *C. xerosis*, *C. hoffmannii*, and *C. diphtheriae*. All yeasts were incubated on carbohydrate broths for identification. When colonies suggestive of *Neisseriae* were found on the plates containing McLeod's medium, they were tested for the "oxidase reaction." Colonies giving a positive reaction were transferred to tubes of dextrose, maltose, and saccharose media which were incubated for forty-eight hours under 10 per cent carbon dioxide tension to differentiate the varieties of *Neisseriae*.

Results

Ninety-six per cent of the cultures were positive. Thirty-eight per cent were positive for one organism; 46 per cent for two organisms; 11 per cent for three organisms; and 1 per cent for four organisms. A total of 167 organisms were isolated in the 96 positive cultures (Table I).

Staphylococci, *Escherichia coli*, and *Streptococcus* accounted for approximately three-fourths (76.5 per cent) of the organisms encountered. Twenty-six varieties of organisms were found.

was from the same maternity service. The most frequently encountered organisms in each series were streptococci, staphylococci, and *Escherichia coli*. However, the order of frequency is different as follows (parentheses refer to Whitacre's series): Staphylococci, 29.9 per cent (17 per cent), *E. coli*, 24.0 per cent (14 per cent), and streptococci 21.6 per cent (54 per cent). The high frequency of streptococci in this comparable series would indicate that, of the three organisms, streptococcus most easily invades the uterus from the birth canal.

In view of the incidence of venereal disease in the mothers of the infants studied, the isolation of only one organism belonging to the Neisserian group was surprising. In the previously mentioned series of Whitacre and associates, 3 per cent of the organisms isolated were of the Neisserian group. Dilution of the contaminating secretion with amniotic fluid or the presence of liquid soap used for lubrication during delivery may possibly interfere with the isolation of the gonococcus from the specimens collected.

Summary

One hundred cultures were taken from the external surface of the eyelids of newborn infants immediately after birth and before the cord was cut. Ninety-six per cent of the cultures were positive, and from one to four organisms were isolated in each positive culture. A total of 167 organisms were identified of which *Staphylococci*, *E. coli*, and *Streptococci* were predominant.

Appreciation is expressed to Frank E. Whitacre, M.D., Professor of Obstetrics and Gynecology, and Anna Dean Dulaney, Ph.D., Assistant Professor of Bacteriology, for assistance in this work.

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TABLE III. INCIDENCE OF HEMOLYSIS AMONG STAPHYLOCOCCI ISOLATED

| NONHEMOLYTIC | | HEMOLYTIC | |
|--------------|--------------------|-----------|-------------------|
| NUMBER | PER CENT OF TOTAL* | NUMBER | PER CENT OF TOTAL |
| 29 | 59.2 | 20 | 40.8 |

*Total of 49 staphylococci (unclassified staphylococcus not included).

Of the total of 36 streptococci identified, 44.4 per cent were nonhemolytic and 55.6 per cent were hemolytic. Alpha- and beta-hemolytic streptococci comprised, respectively, 22.2 per cent and 33.3 per cent of the total (Table IV).

Only one organism encountered belonged to the Neisserian group and this organism did not give a typical fermentation reaction for the gonococcus.

TABLE IV. INCIDENCE OF TYPES OF STREPTOCOCCI ISOLATED

| NONHEMOLYTIC | | ALPHA-HEMOLYTIC | | BETA-HEMOLYTIC | |
|--------------|--------------------|-----------------|-------------------|----------------|-------------------|
| NUMBER | PER CENT OF TOTAL* | NUMBER | PER CENT OF TOTAL | NUMBER | PER CENT OF TOTAL |
| 16 | 44.4 | 8 | 22.2 | 12 | 33.3 |

*Total of 36 streptococci.

Comment

In this series, cultures were taken from the external surface of the eyelids rather than from the conjunctivas. This method was used to demonstrate both the bacterial flora present during parturition and as many varieties of organisms as possible which might contaminate the eyes of the newborn before, during, or after delivery.

It is probable that the incidence of *E. coli* is made high by contamination from the perineal region.

These results demonstrate how the birth canal and, probably to a lesser extent, the perineal region serve as a source of contamination for the eyes of the newborn infant.

If one selects each potential pathogenic organism (hemolytic *staphylococcus aureus*, beta-hemolytic streptococcus, *Monilia albicans*, *Bacterium aerogenes*, gram-negative diplococcus, and members of Colon-aerogenes group) from those listed in Table I, a total of 38 (22.4 per cent) is found. This percentage probably represents a conservative estimate of those which would be capable, under proper conditions, of causing ophthalmia neonatorum.

On the other hand, Sorsby and associates^{3, 4} reported in 1942 and 1944 the organisms detected by smear and culture in 591 cases of ophthalmia neonatorum. Of the organisms isolated in this study, their tables included *staphylococcus albus* (without subdivision), *staphylococcus aureus* (without subdivision), alpha-hemolytic streptococcus, diphtheroid, *corynebacterium xerose*, *corynebacterium Hoffmannii*, and gram-positive cocci. Thus, it is likely that, of the organisms isolated in this study, the percentage capable of causing ophthalmia neonatorum is somewhat above 22.8.

A comparison may be made between these results and those of Whitacre and associates⁵ obtained from uterine cultures taken during the first five days post partum. The two series may be considered comparable in that each

spontaneously after an eight-hour labor. A living female child, weight 1,475 Gm., survived. The placenta showed large plaques of degenerating decidua over most of the maternal surface of the membranes. There was no evidence of marginal placenta previa or of premature separation of placenta.

CASE 2.—A. B., No. 78584, 33 years of age, gravida i, last menstrual period, Sept. 5, 1946, estimated date of confinement, June 12, 1947, previous medical history, negative, basal metabolism plus 13 per cent, Kahn negative, Rh positive. Menstrual history: Periods began at 16 years of age and occurred intermittently and profusely for one year, after which they came every 28-30 days, were of five-day duration and moderate in amount.

The patient was first seen Oct. 25, 1946, at five weeks gestation. She gave a history of having had a tan discharge from October 5 to 12, with recurrence October 23. Examination revealed no bleeding. There was a fibroid about 5 cm. in diameter in the left cornual region. She was given Premarin tablets, one every third day, and Pranone, 20 mg. daily until the end of the fourth month. She was seen again Nov. 19, 1946, because of a history of slight bleeding one day in duration on four occasions since last visit. The fetal heart sounds were heard at four months.

Labor began May 17, 1947 (8 months), was of sixteen hours' duration and was terminated by low forceps delivery. A living female child 44 cm. long, weighing five pounds twelve ounces, survived.

A plaque of degenerating decidua 8 by 9 by 3 cm. was adherent to the maternal surface of the membranes near the edge of placenta. The placenta and membranes were otherwise normal.

CASE 3.—R. O., No. 75654, 30 years of age, gravida i, last menstrual period, Feb. 19, 1946, estimated date of confinement, Nov. 26, 1946, previous medical history, negative, serology negative, Rh positive. Menstrual history: Periods began at 13 years of age, occurred every 28 days for four days. The probable beginning of pregnancy was March 4, 1946. Bright red bleeding was noticed from April 17 to April 27.

She was first seen May 6, 1946, still having a slight tan discharge, and was given Premarin tablets, one every third day, and Pranone 20 mg. daily for three weeks. The bleeding ceased May 27 and did not recur. The fetal heart sounds were heard June 25, 1946 (3¾ months).

Labor began Nov. 10, 1946 (8½ months). The baby, which survived, weighed four pounds and fourteen ounces and the placenta 435 Gm. Several plaques of degenerated decidua were present on the membranes.

CASE 4.—G. B., No. 74185, 30 years of age, gravida i, last menstrual period, March 14, 1946, estimated date of confinement, Dec. 21, 1946, previous medical history, right oophorectomy and appendectomy at 17 years of age (cystic ovary). Basal rate normal, Kahn negative, Rh positive. Menstrual history: Onset of menses at 12-13 years of age, every 28 days for five days with severe dysmenorrhea the first two days.

The patient was first seen Aug. 8, 1946. She gave a history of painless bleeding (bright red) June 9, 19, 29, and July 11, and had been having a continuous brown discharge since July 21. In the last few days before admission she had several gushes of bright red blood, less than during her menses. There were no cramps but uterine contractions were perceptible to the patient. From August 8 to August 30, there were bleeding and cramps intermittently and the uterus was quite irritable. The fetal heart sounds were normal. The patient passed a small mass of brownish tissue August 20. It was reported to be "decidual tissue (degenerated) with chronic inflammatory reaction."

Pregnancy terminated in spontaneous abortion August 30 (5½ months). The placenta, membranes, cord, and a mass of pale tan fleshy tissue were passed en masse.

The placenta measured 9 by 8.5 by 3 cm. The maternal surface was bloodstained and fleshy, with no areas of attached clot. The cotyledons were well demarcated and intact, and the fetal surface was pale and shiny. The membranes were thick and to the maternal surface were adherent plaques of tan, fleshy tissue. The mass of tissue accompanying the placenta

DECIDUAL BLEEDING IN PREGNANCY*

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BLEEDING during the first four to five months of pregnancy frequently presents a puzzling diagnostic problem. If we eliminate threatened, inevitable, and incomplete abortions, tubal pregnancy, premature separation of the placenta, placenta previa, and cervical pathology, there still remains a group of patients who have vaginal bleeding but who seem also to have normally progressive uterine enlargement. The tentative diagnoses are usually those of threatened abortion, premature separation or low implantation of the placenta and, occasionally, placenta previa. Close observation and inspection of the placenta and fetal membranes do not confirm these premises. We have, however, almost invariably found gross evidence of an unhealthy decidua in these patients. The pathology seems to consist in degeneration with leucocytic infiltration of portions of the decidua vera, and, in most instances, a plaque or plaques of such decidua are to be found intimately adherent to the maternal surface of the membranes. A rather careful search of the various texts and the literature offers little or no illumination.

During the last year we have followed thirteen such pregnancies to their termination. We attempt to summarize the clinical and laboratory findings, the end results of these pregnancies, and the therapy instituted.

Bleeding in varying amounts from moderately profuse to slight was present in all these patients. Cramps and bleeding were present in four instances, and when present together justified a poor prognosis for continuation of the pregnancy. The duration of pregnancy after the onset of cramps was four weeks in two instances and six weeks in two other cases. The following case histories are illustrative:

CASE 1.—C. D., No. 73141, 31 years of age, gravida iv, last menstrual period, Dec. 15, 1946, estimated date of confinement, Sept. 22, 1947. Previous medical history, negative, Rh positive, serology negative. Menstrual history, began at 15 years of age, every 28 days for five days. Obstetrical history: 1942, ten weeks, spontaneous abortion. 1943, term, labor, eighteen hours, spontaneous delivery 5½ pounds, stillborn. 1946, six months, premature separation of placenta, stillborn.

This patient was first seen April 7, 1947 (3½ months). She was admitted to the hospital June 30, 1947 (6 months), because of bright red bleeding, accompanied by uterine contractions at frequent intervals with poor relaxation between. The fetal heart sounds were normal. She was given sedation, bed rest, and Lipo-Lutin, 10 mg. three times a day. The bleeding diminished and stopped after three days. Patient was given a transfusion of 500 c.c. citrated blood because of a hemoglobin of 56 per cent. She was then discharged and advised to rest at home. Our tentative diagnosis was that of possible mild separation of placenta.

The patient was readmitted July 22, 1947 (7 months), because of slight vaginal bleeding and was found to be in definite labor. The fetal heart sounds were normal. She delivered

*Read before the Pittsburgh Obstetrical and Gynecological Society, Oct. 6, 1947.

measured 1 to 1.5 cm. in thickness and 13 cm. in length. Microscopic examination revealed placental villi and showed also varying degrees of organization of villi. A considerable amount of decidual tissue exhibiting acute and chronic inflammation was attached to the maternal surface of the membranes. The large mass of tissue consisted of "degenerating decidua with inflammatory reaction."

The fetus measured in length 32 cm. (6 months), weighed 495 Gm., was of male sex, and did not survive. Dilatation and evacuation performed Sept. 9, 1946, for continued lochia rubra produced degenerating decidua.

CASE 5.—D. T., 28 years of age, gravida iii, last menstrual period, July 15, 1946, estimated date of confinement, April 22, 1947, previous medical history, negative, Kahn negative, Rh positive. Menstrual history: Periods began at 15 years of age, and occurred every 28 days for four days. Obstetrical history: 1940, term, five pounds, eight ounces. 1944, term, six pounds, thirteen ounces.

Patient was first seen Jan. 22, 1947 (6 months). She gave a history of bleeding for three days in October, treated by bed rest, and of spotting intermittently since.

She delivered March 28, 1947 (8 months). A male baby weighing five pounds six ounces survived. The placenta appeared normal (475 Gm.). Degenerating decidual plaques were found on the maternal surface of the membranes.

CASE 6.—C. B., No. 69333, 34 years of age, gravida ii, last menstrual period, March 9, 1946, estimated date of confinement, Dec. 16, 1946, previous medical history, negative, Kahn negative, Rh positive. Menstrual history: Menses began at 15 years of age, and were regular every 28 days for six days. Obstetric history: One previous full term pregnancy, 1945.

Patient was first seen Aug. 1, 1946. She began bleeding May 8, 1946, and was admitted to hospital for nine days because of slight intermittent bleeding which continued throughout June and was moderately profuse for the first two weeks of the latter month. The right ovary was enlarged to five times normal size. There was a small adenoma of the thyroid. Proloid, 1 grain (65 mg.) daily, was ordered.

Delivery occurred Dec. 12, 1946. The baby weighed seven pounds, ten ounces and survived. The placenta measured 15 by 15 by 2.5 cm. Its maternal surface was pale, red and fleshy, and the cotyledons were well demarcated and normal. The membranes were thin and translucent and applied to the maternal surface was a large plaque of degenerating decidua approximately 7.5 cm. in diameter.

CASE 7.—P. McK., No. 74551, 20 years of age, gravida i, last menstrual period, Nov. 25, 1945, estimated date of confinement, Sept. 2, 1946, previous medical history, negative, Kahn negative. Menstrual history: Menses began at 14 years of age and were regular every 28 days for five days.

The patient was first seen May 27, 1946 (5 months), and gave a history of moderate bleeding for two days in April, recurring two weeks later in slight amount for several days.

She delivered September 2, 1946. The baby weighed seven pounds, twelve ounces and survived.

The placenta measured 17 by 15 by 3 cm. The maternal surface was dark-red and meaty and the cotyledons were well marked. The membranes were complete, shiny, and on the maternal surface near the placenta were two flat plaques, dark brown in color, measuring 5 and 3 cm. in diameter. Microscopic section of these plaques showed organizing and degenerating decidual tissue.

CASE 8.—I. H., No. 72771, 32 years of age, gravida iv, last menstrual period, Dec. 10, 1945, estimated date of confinement, Sept. 12, 1946, previous medical history, mild hyperthyroidism, duration 16 years, basal plus 17 per cent, serology negative. Menstrual history: Menses began at 13 years of age and occurred every 28 days for five days. Obstetrical history: 1940, 6½ months' pregnancy, hemorrhage ante partum, stillborn. 1942, term pregnancy, normal, low forceps delivery, seven pounds, twelve ounces. 1944, term pregnancy, breech extraction, six pounds, twelve ounces.



Fig. 1.—Cross section of amnion, chorion and degenerated decidua plaque.

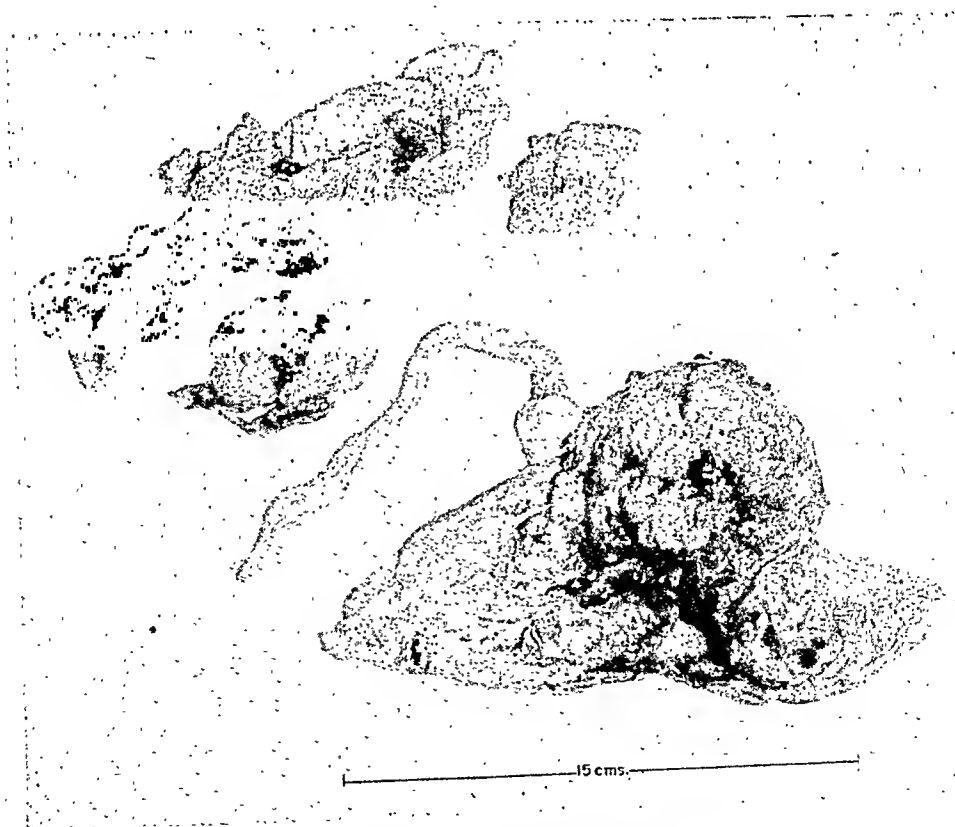


Fig. 2.—Placenta with degenerated decidua on maternal surface of membranes and two large plaques of similar decidua.

serology negative. Menstrual history: Periods began at 12 years of age, and were every 26 days for five days. Obstetrical history: 1942, term pregnancy, normal delivery, eight pounds, four ounces. 1944, term pregnancy, normal delivery, eight pounds.

She was first seen July 30, 1946, and gave a history of slight to moderate bleeding for ten days, beginning July 13. The fetal heart sounds were heard August 20, 1946 (3¼ months).

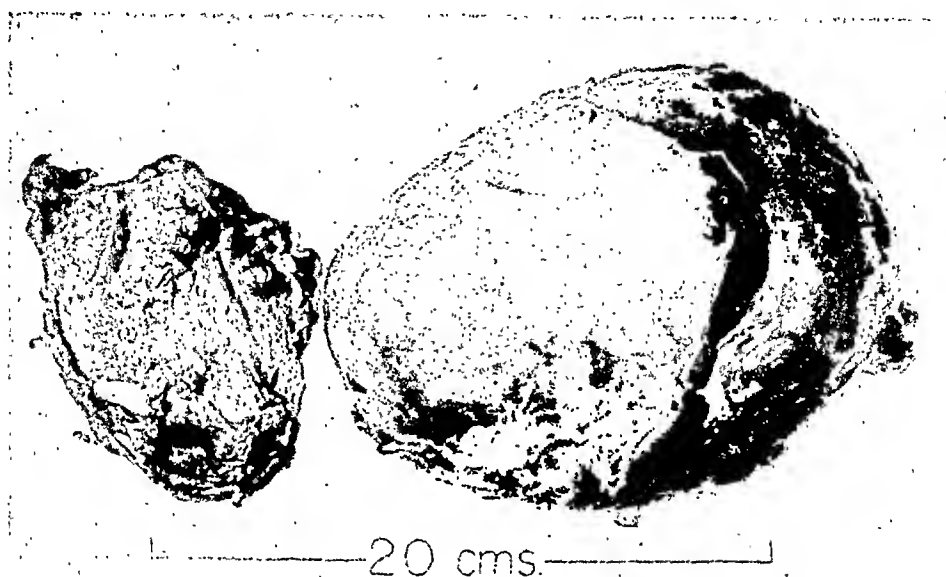


Fig. 4.—Placenta, sac, and enclosed fetus. Membranes entirely covered with thick layer of degenerated decidua.

The patient delivered Jan. 22, 1947. The baby weighed eight pounds, eight ounces and survived.

The placenta was normal in appearance and measured 20 by 18 by 2 cm. The membranes were smooth, pale and glistening. On the maternal surface of the membranes, near the edge of the placenta, there was an irregular plaque of soft brownish-red material 7.5 cm. in diameter, resembling decidua. Microscopic sections through this area showed it to consist of degenerating decidua.

CASE 11.—A. A., No. 49599, 25 years of age, gravida v, last menstrual period, Sept. 12, 1946, estimated date of confinement, June 19, 1947, previous medical history, negative, serology negative, Rh positive. Menstrual history: Periods began at 12 years of age, and occurred regularly every 30 days for five days.

Obstetrical history:

1941, 10 months' pregnancy, normal delivery, six pounds, eight ounces.

1942, 10 months' pregnancy, normal delivery, eight pounds.

1943, 10¼ months' pregnancy, normal delivery, seven pounds, eight ounces. Symptoms of threatened abortion occurred at two months' gestation.

1945, 10 months' pregnancy, normal delivery, six pounds.

She was first seen Dec. 11, 1946 (2¾ months), and later gave a history of having had brown discharge from Dec. 11 to Dec. 31, 1946. The fetal heart sounds were heard Dec. 31, 1946 (3¼ months).

She was delivered June 3, 1947 (8½ months) of a living child. The fetal and maternal surfaces of the placenta were normal. There was a plaque of degenerating decidua 3.5 by 2 by 3 cm. on the maternal surface of the membranes. This was confirmed by microscopic examination.

The patient was first seen March 20, 1946 (3 months). There had been a sudden gush of bright red blood Feb. 25 (2 months), and bleeding had continued intermittently thereafter accompanied by occasional slight cramps.

She was admitted to the hospital May 3, 1946. There was slight bleeding and the uterus was contracting every three minutes. The fetal heart sounds were not heard. A stillborn fetus was aborted spontaneously May 4, 1946 (4½ months).

The placenta showed an unusually thick set of membranes with a heavy layer of dark brown decidua over most of the maternal surface. The placenta itself was normal. Section through the thickened portion of the membranes revealed heavy layers of degenerating decidua.

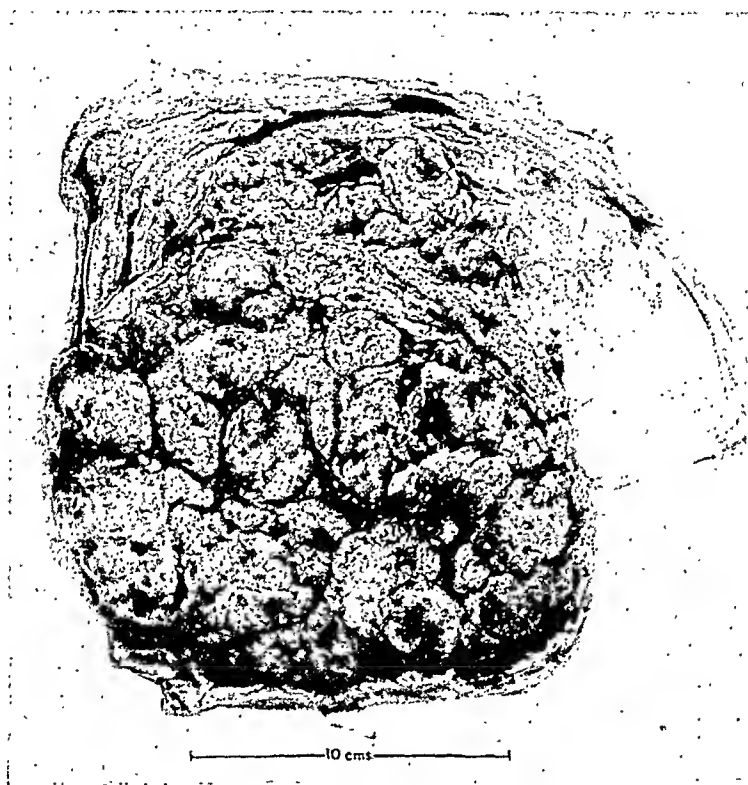


Fig. 3.—Thick layer of degenerated decidua adherent to maternal surface of membranes.

CASE 9.—B. S., No. 76537, 20 years of age, gravida ii, last menstrual period July 20, 1946, estimated date of confinement, May 27, 1947, previous medical history, negative, Kahn negative. Menstrual history: Periods began at 12 years of age, every 28-30 days for five days. Obstetrical history: 1946, 9½ months' pregnancy, breech extraction, six pounds, nine ounces.

The patient gave a history of sudden repeated gushes of blood November 5 to 18 (3 plus months). She was first seen Nov. 19, 1946. December 22 she reported that she had been having intermittent slight dark red discharge. The fetal heart sounds were normal (5 months). There was a small cervical polyp present which was examined and found to be decidual in origin. The patient was admitted to the hospital Jan. 7, 1947, because of increase in bleeding accompanied by slight cramps. The fetal heart sounds were still present (5½ months).

Spontaneous abortion occurred Jan. 8, 1947. The fetus did not survive.

The specimen consisted of a complete placenta, intact membranes and enclosed fetus. The entire maternal surface of the membranes was covered by a thick coat of grayish brown decidua which was moderately adherent and in scattered areas was permeated with blood. Microscopic sections revealed necrotic decidua.

CASE 10.—L. A., No. 26776, 27 years of age, gravida iii, last menstrual period, April 20, 1946, estimated date of confinement, Jan. 27, 1947, previous medical history, negative,

Summary

A series of thirteen patients who exhibited vaginal bleeding during the first four and one-half to five months of pregnancy is presented.

The initial diagnoses included premature separation of the placenta, threatened abortion and fibroid uterus, threatened abortion and low implantation of the placenta.

Seven patients were in the second and six in the third decade of life.

The menstrual history was abnormal in fifty per cent of the patients.

The onset of symptoms began at from four to ten weeks in eleven patients and twelve weeks in two patients.

The bleeding occurred in varying amounts, from slight to moderately profuse in all patients, and was accompanied by cramps and definite uterine contractions in four instances. The onset of the latter symptoms was a poor prognostic sign; the four patients so afflicted aborted in from four to six weeks thereafter.

The pregnancies were of the following duration :

| STILLBIRTHS | | SURVIVED | | | |
|-------------|----------|----------|----------|-----------|------|
| 4½ months | 5 months | 7 months | 8 months | 8½ months | Term |
| 1 | 2 | 1 | 3 | 3 | 3 |

Ten babies survived, 77 per cent. Viable survival, 100 per cent.

There were five primigravidas and eight multigravidas.

One patient was fully ambulatory without any therapy, five were on bed rest alone, and the remaining seven were kept in bed and given estrogen and progesterone therapy.

The final outcome of the pregnancies seemed to depend on the extent of the decidual degeneration. In no instance was there found evidence of subplacental hematomas or gross placental pathology.

Conclusions

Apparently, early bleeding in pregnancy may result from degenerating decidual tissue. This decidual degeneration has seemed to be largely, if not entirely, confined to the decidua vera.

One of the patients in this series presented an apparent cervical polyp, which, on microscopic examination, was found to consist of degenerated decidua, confirming the findings in three cases reported by Haas.¹

Normal progression of the pregnancy, with gradual cessation of the bleeding, examination of any tissue passed, and inspection of the placenta and membranes following delivery will make the final diagnosis.

The early elicitation of fetal heart sounds is of diagnostic and prognostic value.

Conservative management of these patients is indicated. The value of endocrine therapy appears to be questionable.

Reference

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CASE 12.—B. W., No. 79332, 21 years of age, gravida i, last menstrual period December, 1946 (?), estimated date of confinement, September, 1947, previous medical history, negative, serology negative, Rh negative. Menstrual history: Periods began at 16 years of age and occurred every 30 to 60 days for four days.

She was first seen June 30, 1947 (6 months), and gave a history of having had slight bleeding for twelve days at the end of December.

She delivered June 30, 1947. The baby weighed five pounds ten ounces, was 40 cm. in length, and survived (8 months' gestation).

The placenta appeared complete and normal. There was a plaque of degenerating decidua on the maternal surface of the membranes measuring 9 by 7 by 2 cm.

CASE 13.—D. S., 26 years of age, gravida ii, last menstrual period, Nov. 21, 1946, estimated date of confinement, Aug. 28, 1947, previous medical history, the Friedman test was positive Jan. 20, 1947. The patient was given vitamin E and thyroid. The basal reading was minus 25 per cent. Menstrual history: Menses began at 16 years of age and were irregular from onset. Obstetrical history: Previous left salpingectomy for tubal pregnancy.

Bleeding began Dec. 23, 1946, and was slight in amount until Feb. 16, 1947. Profuse bleeding began February 16 and patient was admitted to the hospital for observation. She was discharged March 4, 1947, but continued to have slight bleeding until April 26.

Labor began Aug. 18, 1947, and terminated in the birth of a normal male child weighing six pounds five ounces, which survived. There was a large amount (several plaques) of homogeneous, necrotic, reddish-tan tissue adherent to maternal surface of membranes. Microscopic examination revealed degenerating decidua with inflammatory infiltration.

The essential data regarding these cases may be tabulated as follows:

Age 20 to 34:

In 20's—7

In 30's—6

Menstrual history:

Abnormal, 3 in 20's, 4 in 30's

Normal, 4 in 20's, 2 in 30's

Onset of symptoms:

At 4 to 12 weeks, 11

From 12 weeks on, 2

Duration of pregnancy:

4½ months, 1

5 months, 2

7 months, 1

8 months, 3

8½ months, 3

Term, 3

Initial diagnosis:

Premature separation of placenta, 2

Threatened abortion, fibroid uterus, 1

Threatened abortion, 9

Low implantation of placenta, 1

Therapy:

Ambulatory, 1

Bed rest, 5

Bed rest and endocrine therapy, 7

Gross fetal survival, 10—77 per cent

Viable fetal survival, 100 per cent

Primigravida, 5; fetus survived, 4, stillborn, 1

Multigravida, 8; fetus survived, 6, stillborn, 2

Most of the patients in this series had corroborative roentgenographic findings. In this connection, it may be stated that roentgenographic study should not supplant sigmoidoscopy. The latter frequently reveals intestinal lesions when the former fails to do so. This is due to the inherent limitations of a diagnostic procedure which photographs a column of barium in an intestine which is distended by the liquid suspension. Superficial defects in mucosal pattern due to ulceration, seen early in the disease, are rarely demonstrable either by a barium enema or postevacuation air insufflation film. This point is stressed because the average physician is hesitant to subject a pregnant patient to sigmoidoscopy. It has been our practice to carry out this examination on pregnant women with the patient in the left Sims' position, using a one-half or three-fourths inch sigmoidoscope. Gentle manipulation of the instrument along the rectosigmoidal curves can usually be carried out until about the fifth or sixth month of gestation. After that, it is unwise to insert the instrument beyond the rectosigmoidal junction since the enlarged uterus impinges upon the pelvic colon and rectum. Proctoscopy can be instituted at any time during pregnancy. It is a valuable procedure in experienced hands, since, in the vast majority of cases, the pathological changes in the intestinal wall involve the rectum as well as the rest of the large intestine. No deleterious effects are produced, particularly if, as we constantly instruct our residents, the instrument is held lightly, like the pen or brush of an artist, and no force is used during insertion or manipulation. By introducing the lubricated index finger into the anus and holding it there for a minute or two before instrumentation, spasm is relieved and the procedure rendered relatively comfortable for the patient. Roentgenographic study is essential for the demonstration of the rare segmental proximal colonic lesions, the extent of colonic involvement, luminal stenosis, or concomitant ileitis.

Effect of Chronic Ulcerative Colitis on Pregnancy

Although a detailed obstetric history in every case was lacking, enough data were available to warrant the conclusion that the presence of ulcerative colitis resulted in no ill effects during either pregnancy or labor. The 43 full-term deliveries resulted in live births in every instance. There were no toxemias of pregnancy or fetal abnormalities except in one case. The mother was seen following her first pregnancy, prior to, and during which, she had a severe chronic ulcerative colitis. We succeeded in recovering *B. dysenteriae* Newcastle (Boyd 88) by mucosal crypt aspiration culture of the mother's bowel. The newborn infant developed diarrhea and we isolated the same organism as that found in the mother. Infection probably occurred during passage of the head over the perineum or from the soiled glove of the obstetrician. The baby made an uneventful recovery. This report is of considerable practical interest, since it has been demonstrated that there is no appreciable transplacental passage of antibodies to *B. dysenteriae* from mother to baby.⁴ Newborn infants are quite susceptible to the disease and, if exposed, readily contract it.

Two of the three miscarriages occurred in one patient. There appeared to be no causal relationship between the miscarriages and colitis in either patient. Two therapeutic abortions were performed on one patient before she came under our observations. She had been suffering from severe ulcerative colitis for which an appendicostomy was done. A rectovaginal fistula was also present. Induction of labor was carried out during the sixth month in the case of one patient seriously ill with chronic ulcerative colitis. She subsequently had two pregnancies without untoward results. It is of interest to note that seven of

CHRONIC ULCERATIVE COLITIS AND PREGNANCY

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THERE is a marked paucity of published data concerning pregnancy in women patients suffering from chronic ulcerative colitis. Barnes¹ and Saegesser² report a few cases which they interpreted as possible manifestations of toxemia of pregnancy. Bargaen³ described seventeen patients in whom pregnancy was associated with chronic ulcerative colitis in twenty-two instances.

Material

The present communication concerns 34 women and 50 gestations. These patients were part of a group of 362 men and 421 women with chronic ulcerative colitis under our care, constituting 8 per cent of the total number of women. There were 43 full-term deliveries, 3 miscarriages, 2 therapeutic abortions, 1 tubal pregnancy, and 1 induction of labor during the sixth month. Thirty of the patients under consideration were between the ages of 20 and 31 years and 4 were between 31 and 38 years. In eight instances (23 per cent) the manifestations of chronic ulcerative colitis developed during pregnancy. In seven, this occurred during the first pregnancy and in one during the second. One of these patients subsequently had two pregnancies. In the remaining 26 patients, the chronic ulcerative colitis antedated the onset of pregnancy for varying periods, viz., 3 to 8 months, 5 cases; 1 to 2 years, 6 cases; 2 to 3 years, 4 cases; 4 years, 2 cases; 5 years, 4 cases; 6 to 7 years, 2 cases. In three instances, the disease started during the puerperium, possibly as intramural hospital acute Shigella infections, and all had subsequent pregnancies (one, one, and three).

The disease was regarded as mild in eleven cases, moderate in twelve, and severe in eleven, depending upon the severity of the symptoms and the degree of bowel pathology as visualized at sigmoidoscopy. In general, the basis of classification was as shown in Table I.

TABLE I. SYMPTOMS AND SIGNS IN 34 PREGNANT WOMEN WITH CHRONIC ULCERATIVE COLITIS

| SYMPTOM OR SIGN | MILD | MODERATE | SEVERE |
|--|------------|--------------|-------------------|
| 1. Cramps | Occasional | Intermittent | Constant |
| 2. Bowel movements | | | |
| (a) Frequency (daily) | 3-5 | 5-10 | More than 10 |
| (b) Watery | Usual | Usual | Constant |
| (c) Bloody | Occasional | Frequent | Constant |
| (d) Mucopurulent | Occasional | Frequent | Constant |
| 3. Fever | Occasional | Frequent | Frequent |
| 4. At sigmoidoscopy | | | |
| (a) Granular, bleeding mucosa | Present | Present | Present |
| (b) Lymphoid hyperplasia | Present | Present | Obscured by edema |
| (c) Superficial erosions | Usual | Present | Present |
| (d) Linear and geographic ulceration | Absent | Occasional | Present |
| (e) Pseudopolypoid | Absent | Occasional | Present |
| (f) Mural fibrosis with luminal stenosis | Minimal | Moderate | Advanced |
| (g) Purulent exudate | Present | Present | Present |
| 5. Number of patients | 11 | 12 | 11 |

enhancement of protective antibodies during pregnancy, particularly against *B. coli*, which, with the enterococcus, constitute the chief secondary intramural invaders responsible for the colitis. While conclusive evidence is lacking, it appears that the characteristic remissions and exacerbations in chronic ulcerative colitis parallel relatively high and low degrees of immunity, as reflected in serologic studies on agglutinins and bacteriostatic activity against *B. coli* and enterococcus.⁵ Clinically, exacerbations are often precipitated by upper respiratory infections or similar conditions generally assumed to be associated with lowering of the body resistance. The work of Jeannency, Castanet and Cator⁶ and Frigyesi⁷ tends to support the concept of a rising immunity during pregnancy.

The treatment of chronic ulcerative colitis follows the same general principles in pregnant as in nonpregnant⁵ women except that active immunization against *B. coli* and enterococcus is not instituted after the fifth month. Supportive therapy consists essentially in the parenteral use of 5 per cent dextrose in normal saline or other suitable electrolytes, amino acids (Parenamine), blood transfusions and lyophile plasma, supplemented by a liberal high protein, high vitamin diet without milk.

A discussion of the pathogenesis of chronic ulcerative colitis is not properly within the scope of this presentation except in so far as it concerns the preventive aspects of the disease. It is our belief, predicated upon data presented elsewhere,^{5, 8} that chronic ulcerative colitis and ileitis represent the chronic, non-specific phase of bacillary dysentery. If this premise is acceptable, the implications are clear. Bacillary dysentery is theoretically a completely preventible disease. Intramural outbreaks and contact infections in hospitals are relatively frequent. Pregnant women should receive the proper sanitary and hygienic safeguards. Rectal tubes should be sterilized after use. Persistent diarrhea in a pregnant woman should be promptly investigated by sigmoidoscopy, mucosal crypt aspiration culture and wet smear for cytologic character of the exudate and *E. histolytica*. A purulent cytology generally signifies the presence of bacillary dysentery which also presents a rather distinctive sigmoidoscopic picture. The latter consists of a three-stage progression of pathology, punctate follicular hyperplasia, punctate follicular necrosis, discrete and confluent ulceration on the first, second, and third days, respectively. When positive cultures for the *Shigella* organisms are obtained, proper therapy should be instituted to eliminate them from the mother. A combination of Sulfasuxidine and sulfadiazine or sulfathiazole should be used, each in dosages of 0.25 Gm. per kg. of body weight. If the mother is a persistent carrier, her baby, as well as others in the nursery, should be protected against contact infections. Failure to observe early isolation precautions in diarrheas complicating pregnancy may prove disastrous. This was exemplified in our hospital where mild diarrhea occurred in a mother a few hours after admission but was not noted until one or two days after delivery. *Salmonella panama* was isolated from the feces but the infant had already been infected, and died within a few days. At necropsy, the same organism was isolated from the blood and intestinal contents of the baby.

our patients went through two pregnancies and two through three pregnancies while still in the active phase of the intestinal infection.

Effect of Pregnancy on Chronic Ulcerative Colitis

The status of the patient's colitis was recorded as unchanged, temporarily aggravated, or better. The criteria were the same as those used in Table I. In seven pregnancies (12 per cent) no change was noted; in thirteen pregnancies (30 per cent) the intestinal disease was temporarily aggravated; in twenty-three pregnancies (58 per cent) the intestinal condition was definitely improved, usually to the extent of having few or no intestinal manifestations. These observations apply to both the period of gestation and puerperium. They do not apply, however, to the subsequent course of the disease. In general, it may be said that, compared with nonpregnant controls of approximately the same age, degree of illness, and type of therapy, the subsequent course was almost identical in both groups. There have been no fatalities among the 34 pregnant women. There have been some fatalities among the 387 nonpregnant women (2.8 per cent), but this may be incident to the larger number in the control group. Two pregnant patients deserve special consideration. Both had a severe type of chronic ulcerative colitis but underwent three successful pregnancies following the onset of the colitis. One patient has been completely free of her disease for a period of four years following the birth of her third baby. None of the 34 pregnant women suffered any lasting ill effects from the 43 pregnancies and there was no indication in any case for interruption of gestation, so far as the colitis was concerned. Where there was a temporary aggravation of the intestinal disease (13 pregnancies, 30 per cent), it usually occurred during the first or third trimester and consisted chiefly of an increased number of stools and more profuse intestinal bleeding. It yielded readily to rest and supportive therapy.

Comment

In evaluating the effects of chronic ulcerative colitis on the pregnancy, it appears quite evident that no major obstetric difficulty was encountered in any of the 43 pregnancies occurring in 34 women. In estimating the influence of pregnancy on the ulcerative colitis, it is difficult to escape the conclusion that the colitis was definitely ameliorated in 58 per cent of the pregnancies and unchanged in 12 per cent. If our figures permit broad generalizations, one may assume that in 70 per cent of pregnant women, the presence of chronic ulcerative colitis is certainly no indication for the interruption of pregnancy. In the other 30 per cent, the colitis is only temporarily aggravated and therefore does not militate against the patient going to term. The most striking feature presented by our cases is perhaps not that the patients delivered normally but that almost two-thirds of the pregnancies were associated with improvement of the colitis. The explanation is not obvious. Was the improvement incident to rest, better care, or elimination of disturbing psychological factors? None of these constitutes a valid explanation, or sole explanation, in our cases since the vast majority of our patients in the comparable nonpregnant group appeared to receive the same rest and protective care. Conversely, a number of the pregnant women were definitely annoyed at the additional responsibility involved in having a baby and most of the mothers did not seriously restrict their physical activity until the third trimester. A more valid explanation possibly lies in

CONTINUOUS CAUDAL ANALGESIA

A Report of 1,500 Consecutive Cases

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SINCE the introduction of caudal analgesia by Hingson, Edwards, and Southworth^{1,2} (1942) there have been many individual attempts to evaluate the method. There are, however, no reports of attempts to appraise the value of the method when carried out by resident physicians. With this in mind, the resident house staff has been giving caudal analgesia to suitable patients since July, 1945. The results obtained have been sufficiently gratifying to warrant a comparison with the published reports of more experienced persons.

This report concerns itself with the results obtained in the first 1,500 patients whose labors were conducted under continuous caudal analgesia administered exclusively by the resident house staff. The senior men on the resident staff soon acquired considerable experience in the method so that even though the majority of the caudals were soon being administered by interns, the advice and help of more experienced supervisors were always immediately available.

The over-all success of the method was determined as objectively as possible in each case. An attempt was made to give each caudal a grade. The grades ranged from 100 per cent, when pain was completely relieved between the time when an adequate level of analgesia was reached and the time when the delivery and repair of episiotomy or lacerations were completed, to a zero, when no relief of pain was obtained or when the caudal had to be discontinued prior to completion of the delivery for any reason whatsoever. Cases graded 90 per cent or better were considered as successful, those graded between 50 per cent and 80 per cent as partially successful, and those receiving grades of less than 50 per cent as failures. Segregation of the data in this manner shows that 83.5 per cent of all cases were successful, 3.8 per cent were partially successful and 12.7 per cent were failures. Charting of the results as they were obtained in groups of 100 cases shows that the percentage of successful cases varied from 77 to 93 and the percentage of failures varied from 5 to 21. This demonstrates at a glance what can be expected from caudal when administered by a particular, but changing, house staff. (Fig. 1.)

There were 191 failures in the group. In 98 of these (51.3 per cent) the needle could not be correctly inserted. This figure may seem high, but is only 6.5 per cent of the total number of attempts. In 17 cases, either the needle slipped out of the sacral hiatus, or the tubing became disconnected

Summary

1. An analysis has been presented of 34 patients with chronic ulcerative colitis during 50 pregnancies.

2. Seven pregnancies in five patients did not proceed to term, three of these being operative interferences. All occurred before coming under our observation.

3. Pregnancy was not adversely affected in any of the remaining 43 instances. They resulted in full-term, live births.

4. During 58 per cent of the pregnancies, the ulcerative colitis was definitely improved.

5. From the data presented, it appears that termination of pregnancy is not indicated in the presence of chronic ulcerative colitis.

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120 EAST 39TH STREET

This mortality is so low that a comparison between this group and a comparable group delivered without caudal analgesia seemed necessary. Consequently, the record of all of the labors resulting in the birth of premature infants and conducted without caudal analgesia during the same period of time as our caudal group were analyzed. These results are given in Table II.

TABLE II. PREMATURE INFANTS: CAUDAL ANALGESIA VERSUS ALL OTHER METHODS USED DURING THE SAME PERIOD OF TIME

| WT. (GM.) | NO. | PER CENT ² | I.P. ¹ | P.P. ¹ | PER CENT | N.N. ¹ | PER CENT | TOTAL INFANT MORTALITY PER CENT ³ |
|--|-----|-----------------------|-------------------|-------------------|----------|-------------------|----------|---|
| <i>Caudal Group—1,500 cases. (Total incidence of prematurity, 7.47 per cent)⁴</i> | | | | | | | | |
| 2,001-2,500 | 69 | 63.30 | 0 | 0 | 0 | 1 | 1.44 | 1.44 |
| 1,001-2,000 | 32 | 29.36 | 0 | 0 | 0 | 3 | 9.37 | 9.37 |
| Subtotal | 101 | 92.66 | 0 | 0 | 0 | 4 | 3.96 | 3.96 |
| 500-1,000 | 8 | 7.34 | 0 | 0 | 0 | 6 | 75.00 | 75.00 |
| Total | 109 | 100. | | | | 10 | 9.17 | 9.17 |
| <i>Noncaudal Group—4,123 cases. (Total incidence of prematurity 6.48 per cent)⁵</i> | | | | | | | | |
| 2,001-2,500 | 152 | 63.07 | 4 | 2 | 3.95 | 6 | 3.95 | 7.90 |
| 1,001-2,000 | 73 | 30.29 | 6 | 1 | 9.59 | 14 | 19.18 | 28.77 |
| Subtotal | 225 | 93.36 | 10 | 3 | 5.77 | 20 | 8.88 | 14.66 |
| 500-1,000 | 16 | 6.64 | 8 | 6 | 75.00 | 2 | 25.00 | 100.00 |
| Total | 241 | 100.00 | 18 | 9 | | 22 | 9.96 | 20.36 |

¹I.P. Death during labor.

P.P. Born living, but not surviving long enough to reach nursery.

N.N. Surviving long enough to reach nursery, but dying before discharge from hospital.

²This column gives the per cent distribution of the infants by weight in the caudal and noncaudal group.

³This column gives the per cent mortality within the group.

⁴Incidence includes three infants dead at onset of labor.

⁵Incidence includes 26 infants dead at onset of labor.

In any consideration of differences between two groups, it is, of course, essential that the two groups under comparison be as nearly identical as possible. The total infant mortality in babies living at the onset of labor, in the 101 babies weighing between 1,001 and 2,500 Gm., born of mothers receiving caudal analgesia, was 3.96 per cent, whereas the mortality in the 225 babies in the similar group born of mothers not receiving caudal was 14.66 per cent. This difference is considerable, but it is significant only if no selection of cases, either unintentional or otherwise, was practiced which would favor good results in the caudal group and poor results in the noncaudal group.

In order to establish the essential uniformity of the two groups, the frequency with which prematurity occurred in the two groups and the frequency with which premature babies of a given size appeared in the two groups of prematures was obtained. The incidence of prematures was 7.47 per cent among the 1,500 mothers delivered using caudal analgesia and 6.48 per cent among the 4,123 mothers not receiving caudal. These figures are essentially the same as those reported from other institutions.⁴ There is possibly a significant increase in the number in the caudal group because, as experience accumulated, there was an increased tendency to use caudal when the baby was known to be premature. The number of babies dead prior to onset of labor is relatively greater in the noncaudal group (26 in 4,123 cases, or .63 per cent) than in the caudal group (3 in 1,500 cases, or .2 per cent)

without the knowledge the person managing the caudal soon enough to re-establish the level of analgesia prior to delivery. There were ten failures due to faulty anesthetic agent and another ten failures in which the caudal appeared to be satisfactory, but the patient seemed to be emotionally too unstable to permit continuation of the analgesia. The remaining 56 cases include those in which either an adequate level of analgesia could not be maintained or in which an adequate level was never obtained.

EFFECTIVENESS OF CAUDAL ANALGESIA IN THE MANAGEMENT OF LABOR AND DELIVERY

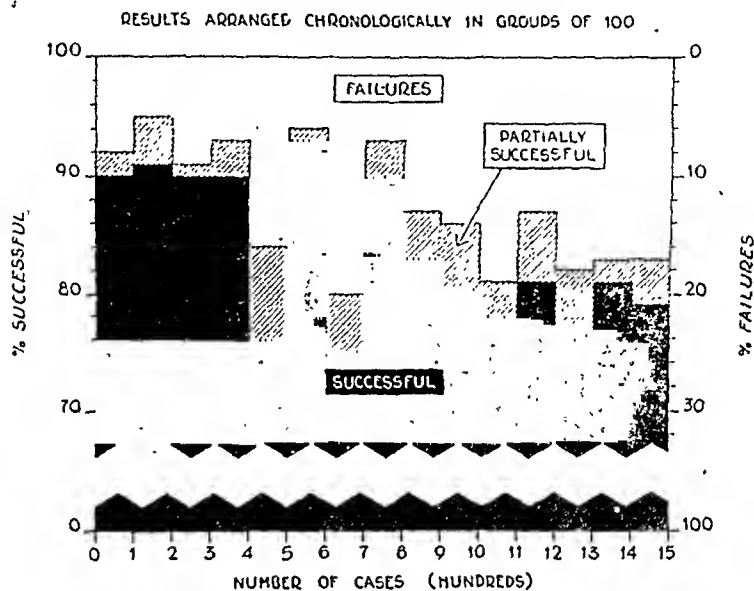


Fig. 1.

In this group of 1,500 deliveries, the effect of continuous caudal on the child was also observed. (Table 1.) One of the reputed advantages of caudal is the promptness of spontaneous cry and respiration of the newborn infant. The results of this study are in complete agreement with that claim. Only 2.5 per cent of the mature children required any resuscitative measures. This figure is quite low, especially when any measure beyond cleaning the nasopharynx with a rubber bulb syringe was considered a resuscitation. Even in the premature group, resuscitation was required in only 6.0 per cent of the group. The figures approximate the figure of 1.9 per cent given by Irving, Berman and Nelson³ for resuscitation in normal deliveries without anesthesia of any sort. The total number of stillborn infants is somewhat below the expected, but this may be due to the fact that caudal was deliberately not used in many cases in which the baby was known to be dead prior to labor.

The good results in the premature baby are striking. There was a total mortality of only 3.96 per cent in the group weighing 1,001 to 2,500 Gm.

TABLE I. BABIES BORN OF 1,500 MOTHERS IN THE CAUDAL SERIES

| SIZE | TOTAL NO. | LIVING | RESUSCITATIONS | STILLBORN | NEONATAL DEATHS |
|-----------------|-----------|--------|----------------|------------|-----------------|
| Full term | 1,410 | 1,382 | 35 (2.5%) | 28 (1.9%) | 9 (0.63%) |
| 1,001-2,500 Gm. | 104 | 101 | 6 (6.0%) | 3 (2.9%) | 4 (3.9%) |
| 500-1,000 Gm. | 8 | 5 | 0 | 0 | 6 (0.75%) |
| Total | 1,522 | 1,491 | 41 (2.7%) | 31 (2.03%) | 19 (1.24%) |

Note: This table includes twenty-two sets of twins born during this series of 1,500 deliveries.

The experience gained in this study has been sufficient to bring to light the majority of complications which may arise. The needle has broken in three cases, in each of which it was necessary to make a short skin incision over the sacrum before the needle could be successfully removed. In two cases, an occult subarachnoid tap occurred so that unintentional spinal anesthesia was obtained. In one of these it was necessary to withdraw spinal fluid through a lumbar tap because 375 mg. of Metycaine had been given. Infection occurred at the site of puncture in five cases and in two of these incision and drainage were necessary. There were seventeen patients in whom the blood pressure was so labile that, despite the use of vasopressor drugs and change in posture, it was deemed wise to discontinue the caudal. Finally, and of not too much importance as judged by the result, a very significant increase in the frequency of delivery by forceps was noted.

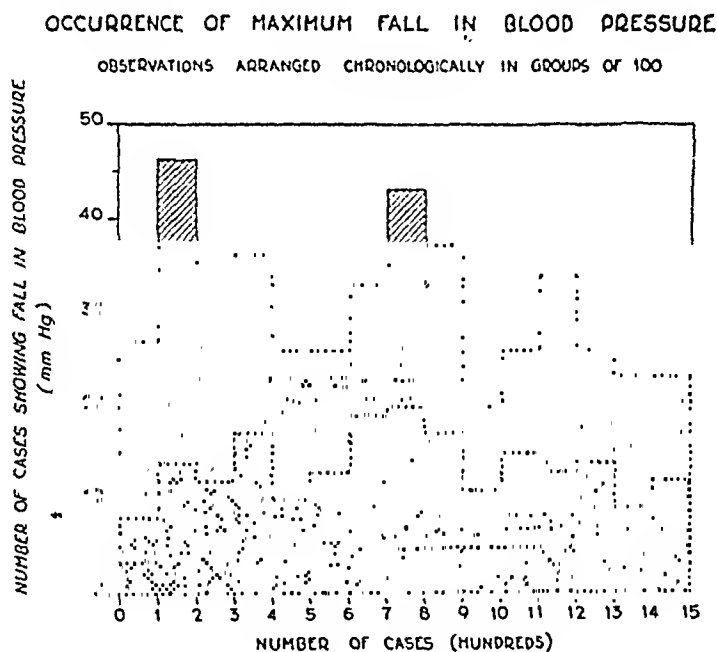


Fig. 2.

One of the most undesirable features of caudal is the fall in blood pressure. A fall in systolic blood pressure to 90 mm. Hg or below was observed in 30 per cent of the cases, and a fall to 80 mm. or lower was observed in 13.6 per cent of the 1,500 cases. This may at first sight seem too high. The results graphed chronologically in groups of 100 (Fig. 2), however, seem to indicate that this is to a considerable extent an inherent and predictable accompaniment of continuous caudal analgesia using this particular analgesic agent (1.5 per cent Metycaine). In the great majority of these cases in which falls in blood pressure did occur, the pressure soon returned to normal levels with no treatment other than change in posture. Usually, when the patient was placed on her side for a few minutes the blood pressure increased rapidly. That this maneuver was highly satisfactory is well shown by the fact that in the last 1,000 cases only 28 patients received vasopressor drugs, whereas in the first 500 cases 57 patients were given vasopressor drugs. The marked decrease in the need for vasopressor agents was probably due to the fact that it soon became apparent that there were fewer cases showing severe depression of the blood pressure when the

because mothers whose babies were known to be dead at the onset of labor were usually not given caudal. These two minor degrees of selection should have no effect on the results obtained. The more important question is one relating to the size of the babies. Were there more premature babies of greater weight in the caudal group than in the noncaudal group? This seems not to have been so. The frequency with which babies of the given weight fell into the three groups was consistent. Babies weighing 2,001 to 2,500 Gm. made up 63.30 per cent of the group whose mothers received caudal and 63.07 per cent of the group whose mothers did not receive caudal. Similarly, in the groups weighing 1,000 to 2,000 Gm. the figures were 29.36 per cent and 30.29 per cent, and in the very small, previable group with weights between 500 and 1,000 Gm. the figures were 7.34 per cent and 6.64 per cent, respectively. This analysis of the two groups serves to establish the essential uniformity of the two groups in so far as weight is concerned.

The results obtained indicate that in premature infants of all sizes, living at the onset of labor, the use of continuous caudal analgesia increases the probability of living throughout the labor and of reaching the nursery alive. All babies in the caudal group lived long enough to reach the nursery. Whereas in the noncaudal group, 5.7 per cent of them either died during labor or lived only a few minutes after birth and, consequently, did not reach the nursery. Secondly, not only are babies more likely to live long enough to reach the nursery, but also their chances of ultimate survival are considerably greater. In the caudal group, only 3.96 per cent died neonatally, whereas 8.88 per cent of the noncaudal group died (1,001 to 2,500 Gm. group). The total infant mortality in infants weighing between 1,001 and 2,500 Gm. at birth was reduced in the caudal group to 3.96 per cent, in contrast to a total mortality of 14.66 per cent in the noncaudal group.

The question, of course, arises concerning the significance of the result. The study has been as objective as possible. All premature infants were cared for in the same nursery without the personnel's being aware of which babies were delivered from mothers receiving caudal analgesia and which were from the noncaudal group. The babies in the two groups were also born during the same period of time. The question regarding significance of the difference between the two groups is, therefore, dependent upon the size of the groups. Are the groups large enough to warrant any conclusions? To get some indication regarding this, the groups were divided into equal parts. There were 323 living premature infants admitted to the nursery during the period of study (not including 27 intrapartum and immediate postpartum deaths, all of which occurred in the noncaudal group). When these are divided chronologically into halves, the caudal group was found to contain 46 prematures with two deaths in the first part and 55 prematures with two deaths in the second group (excluding those infants in the previable group). The noncaudal group contained 111 with 11 deaths in the first part and 101 with nine deaths in the second part. The groups can, therefore, be divided in two approximately equal parts with virtually the same results obtained in each. This, of course, suggests rather strongly that the number of cases is adequate to give results which may be expected to recur regularly and which are presumably significant.

Another question, and certainly a most important one, is whether or not continuous caudal analgesia is a worthy substitute for other methods of analgesia and anesthesia, or, if not a substitute, a worth-while adjunct to them. The answer to this is, of course, dependent almost entirely upon the safety of the method as employed, regardless of the degree of technical competence of the persons giving the caudal.

SPINAL ANESTHESIA FOR CESAREAN SECTION

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(From the Middlesex Hospital)

WE ARE opposed to the use of spinal anesthesia in major obstetric operations as a single injection procedure but as we have employed fractional spinal anesthesia for cesarean operations at Middlesex Hospital since 1941, without a fatality or serious complication attributable to the anesthesia, it seems worth while to report our experience. We have reviewed the cesarean operations done at Middlesex during the past five years; there are 328 consecutive cases. The operations were performed by five general surgeons and the two obstetricians writing this report. Anesthesia was administered by four physician-anesthetists, all of whom have had wide experience with spinal anesthesia, since most of the abdominal operations at our hospital are performed with the aid of "continuous spinal."

The advantages to the surgeon of operating with the aid of spinal anesthesia are too well known to require elaboration. The excellent relaxation of abdominal musculature, lack of bowel distention, absence of straining on the part of the patient are real contributions to the ease of performing unhurriedly an operation in the lower abdomen. Those of us who were trained to do abdominal surgery under inhalation or local infiltration anesthesia do not need to have those advantages emphasized. In the case of a parturient patient, spinal anesthesia offers the important advantage of obtaining maternal anesthesia with no anesthetic effect upon the baby. This is a vital consideration when the operation is to be performed because of premature separation of the placenta or any other condition in which the baby's oxygen supply is dangerously diminished before operation is begun. The chief disadvantage of spinal anesthesia for cesarean operations is that many pregnant women, for some as yet unexplained reason, are unusually sensitive to anesthetic agents placed in the subarachnoid space and a certain number of such patients will develop severe vasomotor collapse if a single dose of 150 mg. of novocain, or similar drug, is so administered. Fractional or continuous spinal anesthesia eliminates this hazard.

Procedure

The patient receives $1\frac{1}{2}$ grains of Nembutal an hour or two before operation and $1/150$ grain of atropine when called to the operating room. When the spinal procedure is about to begin, the blood pressure is determined, after which 50 mg. of ephedrine are administered. With the patient lying on her right side upon a Lemmon's mattress, a spinal puncture is made at the third lumbar interspace, using a special malleable needle which is left in place throughout the operation. 10 c.c. of spinal fluid are withdrawn and mixed with novocain crystals to make a 3 per cent solution. A fine-bore rubber tube is connected with the spinal needle and with the syringe containing the novocain solution. Fifty to 90 mg. of novocain dissolved in spinal fluid are then injected into the subarachnoid space. The patient is placed on her back and her blood pressure determined. If the systolic pressure falls below 100, 2 to 3 c.c. of spinal fluid are

initial induction was carried out with the patient on her back rather than on the side. By this method, a patient whose pressure fell could be treated very promptly and usually effectively by placing her on her side.

The maternal mortality in this group of cases was quite low. There were two maternal deaths, neither in any way due to the type of analgesia used. One patient with eclampsia died of the disease 48 hours after delivery, and a second patient, who had virtually reduced herself to skin and bones by starvation (anorexia nervosa), died three weeks post partum of acute yellow atrophy of the liver. This gives a maternal mortality rate of 1.33 per 1,000 deliveries, a surprisingly low figure when it is recalled that the group of 1,500 included several difficult problems. There were eight patients with severe pre-eclampsia (systolic blood pressures 200 mm. Hg or more) and five patients with actual eclampsia. From this group there were delivered thirteen living (one set of twins) and one macerated infant, all of those born living, surviving. There were also three patients with active tuberculosis, two with severe asthma, and seven with acute respiratory disease ranging from severe bronchitis to bronchopneumonia. Finally, virtually all of the patient encountered with heart disease during the period were given continuous caudal. There was one case of coarctation of the aorta and three with advanced rheumatic heart disease. Two of these were fibrillating and one was in early heart failure. Each of these patients with heart disease and/or pulmonary disease was delivered without incident and without the development of any postpartum complication.

The risk to the mother seems to be no greater than the risk of other forms of analgesia. The risk to the baby is certainly no greater, and in premature infants seems to be materially less. Consequently, there appeared to be no reason for not continuing the study and thereby gaining added experience with this new method of controlling the pain of childbirth and decreasing, if possible, the dangers connected therewith.

Summary

A detailed study has been made of the results obtained in 1,500 consecutive cases receiving continuous caudal analgesia for the management of labor and delivery. In 80 per cent of the cases in which caudal was attempted, the results were entirely satisfactory. Caudal was used successfully in several cases complicated by cardiac and respiratory disease, and in several cases of pre-eclampsia and eclampsia. The most gratifying results were obtained in premature labors. The mortality in premature infants born of mothers receiving continuous caudal analgesia was only one-third as great as in premature infants born of mothers receiving other types of analgesia and anesthesia.

No serious complications have been encountered in this group of cases. The needle was broken in three cases. Occult subarachnoid tap occurred in two cases. Localized infection occurred at the site of puncture in five cases. The systolic blood pressure fell to 80 mm. or below in 13.6 per cent of the cases, but this was usually promptly restored to normal by change in position or vasopressor drugs.

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3. Irving, F. C., Berman, S., and Nelson, H. B.: *Surg. Gynec. & Obst.* 58: 1, 1934.
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Complications having no relation to the spinal anesthesia are listed briefly for what interest they may present as postoperative results obtained after cesarean operations in a 175 bed hospital where the operations were performed by seven surgeons, most of whom have had no special obstetrical training.

Mortality

Two deaths (0.6 per cent), both from embolism. (One patient, a severe essential hypertensive, was advised to have her pregnancy terminated in the first trimester but refused.)

Morbidity

Fifty-four cases (16.4 per cent). (Excluding the first twenty-four hours after operation, two or more rises of the rectal temperature to 100.4° F. or above constituted a morbid convalescence.) Two to four such elevations of temperature were termed "mild" febrile convalescences; there were 24 cases (7.3 per cent). Four to seven elevations above 100.4° were classified as "moderate"; 28 cases (8.5 per cent). Elevations of longer duration were called "severe"; 2 cases (0.6 per cent).

Classification of the causes of the febrile convalescences is as follows: 3 pyelitis, 3 thrombophlebitis, 2 mastitis (one with abscess), 1 active tuberculosis, 1 evisceration (an obese patient who recovered after resuture of the abdominal wall). In the remainder of the cases (44), mostly "mild," there were no specific diagnoses.

Conclusion

Continuous or fractional spinal anesthesia, when administered by a capable physician-anesthetist, is a safe and, in our experience, the most satisfactory anesthesia for use during cesarean operations.

We are indebted to Dr. Joseph Magnano, chief anesthetist, Middlesex Hospital, for critical evaluation of this report.

withdrawn. The pressure almost invariably rises within a few minutes to the normal level and rarely drops again with the subsequent injections of the anesthetic agent which are given in 20 to 40 mg. doses as required during the operation.

Often an infusion of saline with 5 per cent glucose is started about the time the operation begins, since many patients wish to "be asleep" during the procedure and it is a simple matter to administer a small dose of Pentothal through the infusion tube as soon as the baby is delivered. Also, blood or plasma can be started quickly if the surgeon encounters unusual hemorrhage during the operation. One-fourth grain morphine or one-third grain Pantopon and 1 c.c. Pitocin are given to the mother as soon as the child is delivered.

In our series of 328, there were only three cases in which the operation was not completed under spinal anesthesia. In one instance, the spinal needle was dislodged while turning the patient from her side to her back, and there were two cases in which the blood pressure, after an initial drop, did not return promptly to normal levels. In all three "failures," the operation proceeded under cyclopropane anesthesia without incident.

In the series, 59 cases (18 per cent) showed a systolic drop in blood pressure below 100 after the initial dose of novocain had been administered but, with the two exceptions noted above, the pressure promptly returned to normal and subsequently, with two exceptions, no further drop in blood pressure was noted with repeated doses of the novocain solution.

Dosage

There is a wide variation among gravid patients in the total amount of novocain required for satisfactory anesthesia. The average total dose (given fractionally) in our series was 130 mg. with a range in total dosage from 50 mg. to 440 mg. Seventeen cases required 75 mg. or less. This marked difference among pregnant patients in the effectiveness of novocain as a spinal anesthetic points up the reason why the drug should not be used during cesarean operations in the "one shot" (150 mg.) manner. In many of our patients, 150 mg. of novocain would not have been sufficient for adequate anesthesia. In the majority of our patients, 150 mg. would have been more than necessary and, in several cases, such a dose might well have precipitated serious vasomotor collapse.

Babies

All the babies in our series were in good condition on delivery with the exception of eleven. Of these eleven, four were hydrocephalic, three were dead because of extensive premature separation of the placenta, two were dead several days before operation, one was a monster and one had multiple congenital defects. In other words, all babies who were normal at the beginning of cesarean section were in good condition upon delivery.

Complications

There were no serious or permanent maternal postoperative complications which could be ascribed to the effects of spinal anesthesia. As in any series of lower abdominal operations, a few patients required catheterization for 24 hours postoperatively and a very occasional patient required catheterization for a longer time. Postoperative distention was not a serious problem except in one patient who had had an extensive premature separation of placenta and postoperatively developed intestinal obstruction which, however, was relieved by the passage of a Miller-Abbott tube. A few patients were distressed with "spinal" headaches but these were generally only moderately severe and vanished after a few hours. Very occasionally, a spinal headache persisted for a few days.

Toxemia was recorded in 22.69 per cent of the cases. These cases ranged from the mild toxemias to the fulminating, convulsive type. The fetal mortality in these cases was 16.21 per cent. None of the mothers died.

Staining was observed in 14.10 per cent of the cases. Such staining occurred both in the first and second trimesters of the pregnancy. Hormones were administered in one case with cessation of staining. The remaining cases were treated expectantly with bed rest and sedation.

Spontaneous rupture of the membranes occurred in 6.74 per cent of the cases. A history of injury followed by rupture of the membranes was obtained in only two of the cases. In the remaining nine cases there was no history of injury or strain.

RATIO OF PERCENTAGE OF PREMATURE DELIVERIES TO PARITY OF PATIENT

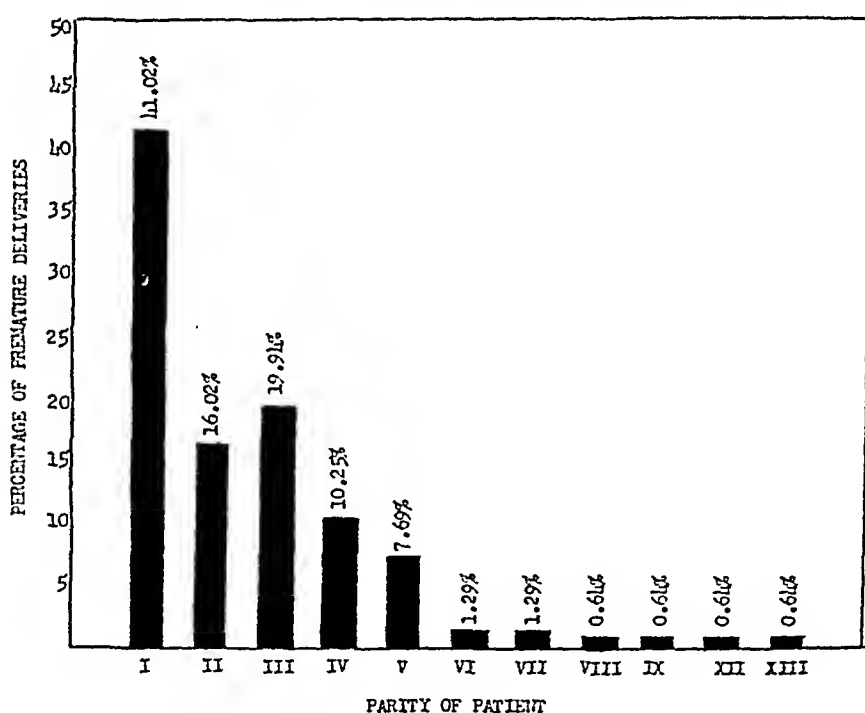


Fig. 1.

Premature separation of the placenta was noted in 4.90 per cent of the cases. Placenta previa occurred in one case.

A variety of other diseases occurred, among which was one case each of pyelitis, renal calculus, bilateral hydronephrosis and hydroureter, congenital heart disease (patent ductus arteriosus), rheumatic heart disease, grippe, bronchitis, Reynaud's disease and scleroderma, scarlet fever (one month prior to delivery) and endometriosis. Appendectomy was performed eight days prior to delivery in one case. There were two recorded instances of fibroid uteri (Fig. 2).

Days Prior to Expected Date of Confinement.—Of these patients, 25.67 per cent were at term; 48.64 per cent were about 60 days from term; 8.10 per cent were about 90 days from term; while 4.05 per cent were about 120 days from term. The expected date of confinement could not be accurately determined in 13.54 per cent of the cases. These patients were unable to state with any degree of accuracy the date of their last menstrual periods.

Multiple Pregnancy.—Multiple pregnancy occurred in 10.98 per cent of the total number of births. All were twin births. Female twins occurred in 78.94

THE PREMATURE INFANT

A Study of One Hundred Seventy-Three Liveborn Premature Infants

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THIS paper is based on a study of 7,332 deliveries occurring between the years 1939-1944. During that period, there were 173 living premature infants born, an incidence of 2.35 per cent. The highest incidence of premature delivery occurred in 1944 when 3.22 per cent of 1,487 deliveries were premature (Table I).

The records were reviewed with regard to both the maternal factors involved, and the condition of the infant at birth and at discharge from the hospital. Consequently, the paper has been divided into two parts—the first concerned with the maternal factors; the second with the infant.

TABLE I. NUMBER OF PREMATURE INFANTS DELIVERED BY YEARS. NUMBER AND PERCENTAGE OF FETAL MORTALITY BY YEARS

| YEAR | TOTAL NUMBER OF DELIVERIES | NUMBER OF PREMATURE INFANTS BORN | PERCENTAGE OF PREMATURE INFANTS | NUMBER OF PREMATURES DYING | PERCENTAGE OF PREMATURES DYING |
|-------|----------------------------------|---|--|-------------------------------------|---|
| 1939 | 856 | 17 | 1.97 | 6 | 35.29 |
| 1940 | 969 | 21 | 2.17 | 6 | 28.57 |
| 1941 | 1067 | 20 | 1.87 | 5 | 25.00 |
| 1942 | 1431 | 37 | 2.58 | 4 | 10.81 |
| 1943 | 1522 | 30 | 1.97 | 9 | 30.00 |
| 1944 | 1487 | 48 | 3.22 | 9 | 18.75 |
| Total | 7332 | 173 | 2.35 | 39 | 22.54 |

The records are taken from both private and clinic cases, and no attempt has been made to segregate the two types of patient.

Maternal Factors

Age.—The average age of the mothers was 29.9 years. The youngest was 17 years; the oldest 45 years.

Gravida.—Of the women studied, 41.02 per cent were primigravidas. It was noticed that, as the parity of the patient increased, the probability of a premature infant decreased (Fig. 1). In the higher multipara, the occurrence of a premature infant was almost negligible. In the primigravid women, 42.18 per cent of the patients were 27 years of age or over; while 25 per cent of them were 30 years of age or over. It would appear that the older primiparas show a larger proportion of premature deliveries than do the younger primiparas.

Past History.—Of the cases studied, 15.38 per cent gave a history of previous miscarriage or premature delivery.

Prenatal History.—The records were reviewed with particular regard to the prenatal history (Fig. 2). In 39.87 per cent of the cases, no abnormalities of any kind were recorded. Urinalysis and blood pressure were within normal limits; weight gain was not excessive, and the patients did not complain of edema, urinary difficulties, headaches, dizziness or epigastric distress.

eases, 89 per cent were listed as having a normal prenatal course. Perhaps some correlation exists between the psychological well-being of the expectant mother and the incidence of premature deliveries.

Fetal Factors

Mortality.—There was an average of 22.54 per cent deaths for premature infants in the cases studied. Births and deaths by weight have been tabulated and are shown in Table III. (The weight of these infants was recorded in pounds, and the author has retained those figures, although also converting the weight to grams.) In the conversion of pounds to grams, 450 Gm. have been used as being equal to one pound. The results obtained in this study are in accord with those published by Breese,¹ namely, that the weight of the child is the most important single factor in prognosis. As the weight of the child increases, the mortality factor decreases. There was a 100 per cent mortality observed in children born weighing $1\frac{1}{2}$ pounds (675 grams) or less, while those weighing between $4\frac{1}{2}$ and $5\frac{1}{2}$ pounds (2,025-2,475 Gm.) showed but a 7.14 per cent mortality.

TABLE III. NUMBER OF BIRTHS AND DEATHS BY WEIGHT

| WEIGHT | (675 GM.) $1\frac{1}{2}$ LB. OR UNDER | (675-1225 GM.) $1\frac{1}{2}$ - $2\frac{1}{2}$ LB. | (1225-1575 GM.) $2\frac{1}{2}$ - $3\frac{1}{2}$ LB. | (1575-2025 GM.) $3\frac{1}{2}$ - $4\frac{1}{2}$ LB. | (2025-2475 GM.) $4\frac{1}{2}$ - $5\frac{1}{2}$ LB. |
|--------|---|---|--|--|--|
| Births | 4 (2.31%) | 14 (8.09%) | 29 (16.76%) | 70 (40.46%) | 56 (32.35%) |
| Deaths | 4 (100%) | 11 (78.57%) | 12 (41.37%) | 8 (11.42%) | 4 (7.14%) |

The largest number of infants (40 to 46 per cent) born weighed between $3\frac{1}{2}$ and $4\frac{1}{2}$ pounds, and the mortality rate in this group was 11.42 per cent.

It would appear that certain of these infants, particularly those weighing between $4\frac{1}{2}$ and $5\frac{1}{2}$ pounds (2,025-2,475 Gm.), could well be called immature rather than premature infants.

Length of Babies.—The average length of the infants was 17.54 inches. The shortest infant was 12 inches long; the longest 20. The largest number (30.95 per cent) measured 18 inches.

Initial Temperatures.—Rectal temperatures were taken on all of the infants, and an average initial temperature of 96.96° F. was obtained. Twelve infants had temperatures of 100° F. or over. The highest recorded temperature was 102° F. The temperature in the majority of cases rose on the second day to 99° F., and maintained it. Infants showing a slow rise in temperature up to 99° F. usually had a more difficult time than those in whom the temperature rose on the second day.

Initial Weight Loss.—The average initial weight loss was 3.38 ounces. Of the infants, 40.4 per cent showed no initial weight loss. The greatest weight loss was 25 ounces. This occurred in an infant weighing 4 pounds 12 ounces at birth. The child survived and was discharged on the fifty-eighth hospital day.

Length of Hospital Stay.—There was an average of 11.9 days spent in the hospital following delivery. The longest period of hospitalization noted was 87 days; the shortest 7 days.

Weight Gain on Discharge.—These infants gained an average of 9.7 ounces during their hospital stay. Once the initial weight loss had been overcome, the weight gain was progressive.

There was one recorded instance of diarrhea in this group; the remainder of the infants averaged two to three stools daily.

TORSION OF THE HYDATID OF MORGAGNI*

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ONE frequently observes small pedunculated cystic structures in the region of the tubal fimbriae. These appendages, known as the hydatids of Morgagni, usually arouse little more than passing attention. In 1906, Kelly¹ remarked that, although he had seen a variety of interesting affections associated with such structures, he had never observed a condition which could interfere with health. He then described true knots along the pedicle without interference with circulation, strangulation of a portion of the fimbria, hemorrhagic infarction due to twisted pedicle, and adhesions of the hydatid to the sigmoid. In the same year, Boldt² reported a large hydatid (3 by 3¾ inches) with torsion of 180 degrees, involving the tube. The only complaint was left lower quadrant pain. In 1910, Grauert³ operated upon a patient for chronic appendicitis, only to find a plum-sized right hydatid twisted 360 degrees on its pedicle. Subsequently, Andrews⁴ in 1912, Waters⁵ in 1919, and Abernathy⁶ in 1929 reported acute symptoms associated with torsion of the pedicle of the vesicular appendage, each believing his case report to be the first in the literature. To date, a careful review of the world literature reveals twenty-one references to torsion of the hydatid of Morgagni (Table I), although, in four instances, no details are available. (Kelly,¹ Meigs,⁷ and Waugh⁸). In spite of these reports, Novak,⁹ in 1947, states that the hydatid has no especial clinical significance except in very rare instances of intestinal angulation and obstruction caused by a long pedicle.

Case Reports

To the cases already reported, we are adding five more. These were patients operated upon at Michael Reese Hospital during the past ten years, three in our private practice. By analyzing this total of twenty-two case reports, in which more or less complete information is available, we hope to present a clinical picture by which torsion of the hydatid of Morgagni can be recognized. In no instance to date has the possibility of such pathology been entertained pre-operatively. However, since three such cases were reported as having been operated upon at the Mayo Clinic within a two-year period and four of our five patients within a three-year period, the condition must be more common than the literature indicates.

Typically, the hydatid of Morgagni is a small oval or spherical structure about 8 mm. in diameter. Often there is an area of constriction in the mid-portion that produces a dumbbell or beanlike shape. It is usually single but may be multiple. It may be sessile or have a pedicle up to 12 cm. long, although the average length is about 3 cm., and the average thickness is 2 mm. While the exact origin is still debated, it is usually accepted that these cysts represent the persistent cephalad portion of the Wolffian duct. According to Gardner, Greene and Peckham,²⁰ these cysts arise from mesonephric tubules

*Read at a meeting of the Chicago Gynecological Society, Nov. 21, 1947.

The feeding of these infants varied with the individual pediatrician. All infants, however, were given vitamin K intramuscularly following delivery. Vitamin K was not given to the mothers before delivery.

Autopsies were performed on nine of the infants who died. Atelectasis was reported as the cause of death in three cases. Atelectasis plus cerebral hemorrhage were given as the cause of death in two cases. Cerebral hemorrhage plus pneumonia accounted for two deaths; pneumonia alone was responsible for one death; and edema of the pia-arachnoid plus congestion of liver, spleen, kidneys and both adrenal medullas accounted for one death.

Summary

A study of 173 premature infants is presented. Maternal factors and fetal factors are recorded.

Premature delivery occurred most frequently in primigravidas in the older age group.

Over one-third of the cases studied showed no abnormalities during the prenatal period. Toxemia was recorded in approximately one-fifth of the cases. One-sixth of the cases gave a history of staining. Spontaneous rupture of the membranes with and without history of injury and premature separation of the placenta was observed in approximately 10 per cent of the cases.

One-quarter of the patients (25.67 per cent) were at term. Approximately 50 per cent were about 60 days from term.

Multiple pregnancy occurred in 10 per cent of the cases.

Delivery from below was effected in 85 per cent of the cases. Cesarean section was performed in 15 per cent.

Fetal mortality was highest in cesarean section (40.7 per cent); next highest in breech extraction (37.5 per cent). Vertex presentation was accompanied by a fetal mortality of 21.2 per cent. The average length of labor was 7.98 hours.

The highest percentage of premature deliveries occurred in the year 1944, and the majority of these after June 6, 1944. The possibility of psychogenic factors in premature delivery must be considered.

An average fetal mortality of 22.54 per cent was observed. It was noticed that as the weight of a child at birth increased, the probability of death decreased.

Length, weight, and initial temperature of the infants are recorded.

Initial weight loss, length of hospital stay, and weight gain on discharge are recorded.

Autopsy reports on nine cases are summarized.

Reference

1. Breese, B. B., Jr.: J. Pediat. 12: 648, 1938.

TABLE

| NO. | YEAR | AUTHOR | AGE | SYMPTOMS | | |
|-----|----------------|---|-----|--|---------------------------|---|
| | | | | PAIN | NAUSEA AND VOMITING | MISCELLANEOUS |
| 1 | Before 1906 | Kelly | | | | |
| 2 | 1906 | Boldt | 43 | Left lower quadrant, 2 years | | Dysmenorrhea |
| 3 | 1910 | Grauert | | Right lower quadrant, long time | | |
| 4 | 1912 | Andrews | 36 | Right lower quadrant, 5 days | 0 | |
| 5 | 1919 | Waters | 18 | Left abdomen, cramp-like, watched 5 days | + | Dysmenorrhea, |
| 6 | 1929 | Abernathy | 33 | Right lower quadrant, 3 weeks, colicky | | Similar attack 8 years before |
| 7 | 1930 | Okinczye ¹⁰ | | Right lower quadrant, 5 hours, severe, sudden, general at first | | |
| 8 | 1931 | Heinrich ¹¹ | 15 | Lower abdomen, cramp- like, tender right side, 1 day | + | Dysmenorrhea, |
| 9 | 1934 | McDermott ¹² | 16 | General abdominal, right lower quadrant 5 hours, rigid right lower quadrant | | |
| 10 | 1936 | Mugnai ¹³ | 23 | Left lower quadrant, colicky, 1 year | | |
| 11 | 1936 | Tailhefer ¹⁴ & Adrianopoulo | 30 | Abdominal pain, 15 days, location left lower quadrant, cramplike | | |
| 12 | 1936 | Tractenberg ¹⁵ | 29 | Abdominal pain 2 months, tender left lower quadrant | + | Mass palpable, dis- tention, rebound |
| 13 | 1937 | Gregorová ¹⁶ | 38 | Right lower quadrant pain, 1 yr. repeated attacks | + | Distention 4 months mass palpable |
| 14 | 1937 | Zener ¹⁷ | 13 | Sudden attack abdominal pain, right lower quadrant | + | Tender McBurney's point |
| 15 | 1937 | Zener | 34 | Severe, left-sided cramp- like | | Palpable mass, dysmenorrhea, |
| 16 | 1938 | Bowles ¹⁸ | 16 | Right lower quadrant, 6 months (Mentioned by Bowles) | + | Distention, rigid McBurney's point |
| 17 | | Meigs | | | | |
| 18 | 1939 | Waugh | 22 | Right lower quadrant, 24 hours, persistent | 0 | McBurney tender and rebound |
| 19 | 1939 | Waugh | | | | |
| 20 | 1939 | Waugh | | | | |
| 21 | 1943 | Howser and River ¹⁹ | 14 | Right lower quadrant, 19 hours, cramplike | + | Tender McBurney's point becoming rigid 8° |
| 22 | 1947 | Reis and DeCosta | 35 | General abdominal, 12 hours, achy | 0 | Tender right umbil. |
| 23 | 1947 | Reis and DeCosta | 28 | Severe left lower quadrant pain, few hours | | Cyst left, felt 6 months before |
| 24 | 1947 | Reis and DeCosta | 38 | 0 | 0 | Walked into hospital |
| 25 | 1947 | Reis and DeCosta (d) | 23 | Right lower quadrant, moderate, 3 months especially 1 week | 0 | Walked into hospital, not acutely ill |
| 26 | 1947 | Reis and DeCosta (e) | 33 | Right lower quadrant, intermittent, 15 years, especially 3 months | N | Walked in, not acutely ill. |

(d) Courtesy Dr. Irving Stein.

(e) Courtesy Dr. Herman Strauss.

or duets or from paramesonephric structures. Since other broad ligament cysts, whether intraligamentous or pedunculated, may have similar origins, they believe it desirable to avoid such terms as hydatid of Morgagni, Kobelt cyst, or parovarian cyst, and to base the terminology solely on microscopic findings. Unfortunately, in the cases herein reported, this is impossible since these structures were all necrosed. Thus, we can only refer to them as cystic appendages, commonly known as hydatids of Morgagni.

When torsion occurred, pain was the most frequent complaint. In at least one instance, however, pain was lacking, although a tiny twisted gangrenous hydatid was found incidentally during unrelated surgery. At the onset the pain was often diffuse, later becoming localized to the right or left lower quadrant. The intensity varied from mild to severe and the duration from a few hours to days. The only characteristic quality of the pain was its colicky or cramplike nature, which was noted by almost all authors. Not infrequently, an antecedent history of previous attacks, over a period of from weeks to years, was elicited. In about 25 per cent of the patients, onset of dysmenorrhea dated from the first attack of pain. Such dysmenorrhea has been observed to disappear following removal of the hydatid. Nausea and vomiting occurred in 50 per cent of all patients.

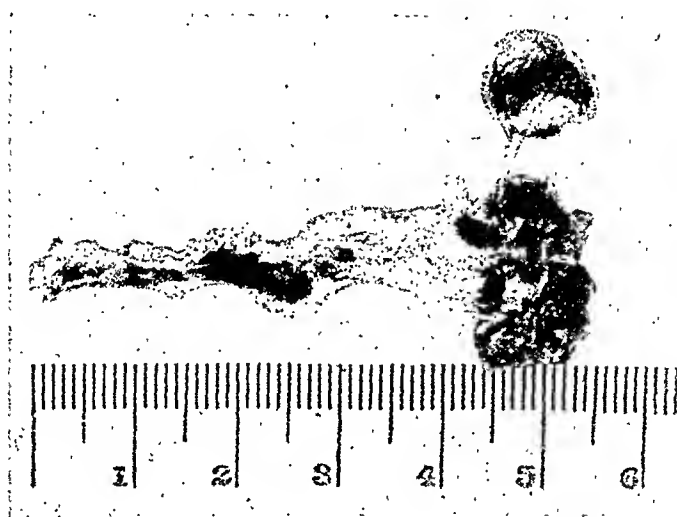


Fig. 1.

Physical examination was not significant. Some patients were acutely ill and evidenced considerable discomfort but no patient appeared seriously ill. The abdomen was occasionally distended, usually tender, and sometimes rigid over the involved area. In only three instances did the temperature exceed 101° F. or the pulse 100. Leucocytosis varied from 9,200 to 21,000, averaging about 15,000. There was no correlation between symptoms, findings, and blood count.

In fourteen of the twenty-two cases, the hydatid was right-sided. This apparent predilection for the right is probably indicative of greater anxiety over right lower quadrant pain because of fear of appendicitis. As a result, exploratory operation is more frequently performed for right-sided complaints and more right-sided twisted hydatids are discovered. Left-sided involvement was variously diagnosed as left-sided appendicitis, twisted left ovarian cyst and ectopic pregnancy.

Of twenty patients in whom the age is known, the youngest was thirteen and the oldest forty-three, with eleven patients under thirty. Five patients were pregnant from two to seven months. Still, we do not believe that pregnancy is a predisposing factor. Rather, pregnant women probably are more concerned about themselves and their physicians are more solicitous.

Examination of the removed tissue has yielded little information indicative of etiology since such tissue is generally necrosed and difficult to recognize as any specific structure.

Torsion of a hydatid, even when associated with gangrene, does not lead to serious intra-abdominal disease. Since the tissue involved is small and usually not adherent to the bowel, one can expect aseptic necrosis to occur with slight degrees of peritoneal reaction. No patient has ever been known to die from failure to operate upon a twisted hydatid. It is probable that patients occasionally operated upon with a diagnosis of acute appendicitis actually suffer from a small twisted gangrenous hydatid which is overlooked. The McBurney incision does not lend itself to thorough inspection of the pelvis. The frequently reported presence of serosanguineous fluid in the abdomen should make one very suspicious of pathology other than the appendix. With bloody peritoneal fluid, the adnexae must be inspected, including the fimbriated region.

Clinically, the five patients we report fall into three classes. Two suffered acute pain, without nausea and vomiting, and were operated upon within a few hours. One was diagnosed as acute appendicitis and the other as a twisted left ovarian cyst. Two other patients complained of intermittent right lower quadrant pain over a period of years. These patients were not in acute distress on admission and were studied in the hospital prior to surgery. One was diagnosed, after transabdominal pneumoperitoneal roentgenogram, as a twisted right ovarian cyst. The other was considered to have recurrent appendicitis. This patient had a gangrenous left-sided hydatid although pain was referred solely to the right side. The last patient presents a unique situation. She entered the hospital without abdominal distress, for hysterectomy because of fibroids. The finding of a small, twisted, gangrenous hydatid was incidental. It points out, however, that asymptomatic gangrene can occur.

Bimanual findings were not helpful. In one patient, previously known to have a cystic adnexal mass, the diagnosis was twisted ovarian cyst. The mass proved to be a large hydatid of Morgagni. In the other patients, there was only tenderness. On abdominal palpation, tenderness was noted in either right or left lower quadrant. Rectus muscle rigidity was not observed in this group.

A gangrenous hydatid was removed from each of these patients. The size varied from 5 to 25 mm. and the pedicle from 10 to 25 mm. In no patient did the temperature exceed 100.2° F., and in only one was the pulse over 100. The two patients with acute symptoms had white blood counts of 13,000 to 19,400, while the other three were from 9,300 to 9,750.

Conclusions

1. The symptoms arising from torsion of a hydatid of Morgagni closely resemble those of acute appendicitis, if right-sided. The pain, however, is usually colicky and has been intermittently present over a period of time. The patient is usually not so sick as to seek early medical care. Nausea and vomiting are frequently present. The temperature usually is less than 101° F. and the pulse under 96.

I

| PREGNANT | PRE-OPERATIVE DIAG. | | | TEMP. | WHITE BLOOD COUNT | PULSE | OPERATIVE FINDINGS | | |
|-----------|---------------------|-----------------|----------------------------|---------------------|-------------------------|-----------|--------------------|------|-------|
| | APPEN- DICITIS | TWISTED CYST | MISCELLANEOUS | | | | RIGHT | LEFT | FLUID |
| | | x | | | | | | x | |
| | x | | | | | | x | | |
| 6 months | | x | | 98.6°F. | | 80 | x | | |
| | x left sided | | or hemorrhage into cyst | to 101°F. | 16,800 | to 130 | | x | x |
| 2 months | | | Abortion Oophor- itis | 99.4°F. | | 80 | x | | |
| | ? x | | or tubal pregnancy | 35.9°C. | | | x | | x |
| | ? x | | | 100.8°F. | 9,200 | 92 | x | | |
| | x | | | 99°F. | | 96 | x | | x |
| | | | Adnexitis, Tbc. | | | | | x | |
| 2½ months | | | No. definite diagnosis | 40°C. | | 100 | x | | |
| | | | Ectopic pregnancy | 101.2°F. | 13,500 | 120 | | x | x |
| 4 months | | x | | | | | x | | |
| | x | | | | 14,600 | | x | | x |
| | | x | | | | | | x | |
| | x | | | 99.6°F. | 21,000 | | x | | x |
| | x | | | | 12,000 | | x | | |
| | x | | | 99.8°F. | 16,500 18,500 | 68 74 | x | | x |
| 7 months | x | | | 99.6°F. | 19,400 | 96 | x | | |
| | | x | | 100.2°F. | 13,600 | 116 | | x | |
| | | x | Fibroids | 100.2°F. 99.8°F. | 9,300 9,700 | 90 92 | x x | | |
| | x | | | 98°F. | 9,750 | 72 | | x | |

The second: Mrs. J. K., Aged 30 years, para 0, Gravida 0, was first studied by the genitourinary service with negative findings. She had knifelike, spasmodic pain in the left lower quadrant. On posterior colpotomy incision, a walnut-size hydatid, twisted on its pedicle from the left tube, was found lying in the cul-de-sac.

The third patient: Mrs. J. A., age 31 years, para i, gravida ii, entered the hospital at the beginning of her ninth month of pregnancy. She complained of nausea, vomiting, and knifelike pain in the right side at the level of the umbilicus. Her temperature was 100.2° F. and her white blood cell count 16,000. Acute appendicitis was diagnosed and she was operated upon through a muscle-splitting incision. The appendix was found normal and was left in; a walnut-sized twisted hydatid was removed from the right tube. She delivered normally, thirty-six hours later, and made an uneventful recovery.

DR. R. R. GREENE.—The term "paramesonephric duct" makes good sense. Gruenwald has very beautifully demonstrated that its advancing tip grows under the basement membrane of the mesonephric duct. He has also shown that its normal development is dependent on the presence of the mesonephric duct.

The development of the oviduct fimbria is a very complex process. Because of this very complexity, aberrant epithelial structures of paramesonephric origin are frequently found in or on the broad ligament. The "hydatid of Morgagni" or better termed "pedunculated paramesonephric cyst" is such a structure. Its mode of origin can easily be demonstrated in the embryo. In properly prepared tissues from the adult, its paramesonephric derivation also can be easily demonstrated. Its epithelium is identical to that of the oviduct and is distinctly different from that of mesonephric tubule or mesonephric duct origin.

The differences between the epithelia of paramesonephric and mesonephric origin have been discussed in some detail in a publication by Drs. Gardner, Greene, and Peckham in a recent issue of this Journal.

DR. REIS (Closing).—The occurrence of these twisted cysts of Morgagni or mesonephric remnants in the course of several years stimulated us to make this report. We hope to find out whether they are as infrequent as the literature leads us to believe. Secondly, we would like to emphasize that, when the patient is operated upon for what seems to be a ruptured appendix or a twisted ovarian cyst and nothing is found, it is much more satisfying to find the cause of the trouble to be a twisted hydatid of Morgagni rather than to close the abdomen without having found any pathology to account for the symptoms for which the laparotomy was performed.

2. The pelvic organs should be examined at every laparotomy. This becomes increasingly important when serosanguineous fluid is encountered. If a McBurney incision has been used, it may require extension to make such examination possible.

3. Pedunculated hydatids of Morgagni encountered during surgical procedures should be removed prophylactically.

4. Torsion and even gangrene can occur with few if any complaints.

5. Although only a total of twenty-six cases of torsion of the hydatid of Morgagni have been reported, the condition probably occurs fairly frequently; at times it may be overlooked, at other times misdiagnosed.

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Discussion

DR. FRED O. PRIEST.—The pedunculated hydatid is relatively common as seen in pelvic surgery. Torsion with acute symptoms might be expected to be relatively common but this is not true. In reviewing the records at the Presbyterian Hospital, I could find only three cases occurring since 1930. In none of them was a correct preoperative diagnosis made, acute appendicitis or twisted ovarian cyst being suspected. The fact that more have been found on the right side is probably due to the fact that "right-sided" abdominal pain is regarded more seriously and surgery is advised, while pain in the left lower quadrant is often treated conservatively.

The presence of straw-colored or blood-tinged fluid was not mentioned in any of the three operative records that I am reporting. The presence of such fluid, varying from a few cubic centimeters up to one ounce or more, was recorded over a period of two years. We found that it bore a definite relationship to the age of recent corpora lutea, whether or not hydatids were present.

The first of our patients: Mrs. E. K., aged 27 years, para 1, gravida 1, had had 4 previous attacks of colicky pain in the right lower quadrant. Nausea and vomiting occurred with the attack. On admission, her temperature was 99.2° F., her white blood cell count 12,000, and there was moderate rigidity in the right lower quadrant. A plum-size gangrenous hydatid and a normal appendix were removed at laparotomy.

Although there have been no adequate clinical tests to differentiate false from true incontinence, the following therapeutic method has proved satisfactory. It can be used as an aid in selecting cases of incontinence which require surgery. In many cases the incontinence may be cured by this method alone. Incontinence may return as a result of a recurrence of the original inflammatory lesions.

A course of treatment by dilatation of the urethra with graded Hegar dilators from No. 6 to No. 9 is given once weekly. After the urethra has been dilated for approximately five minutes, the bladder is emptied with a catheter, and 5 per cent silver nitrate on a long applicator is applied topically, with or without an endoscope, to the trigone, bladder neck, and urethra, as described by Oberlander⁵ and Kelly and Burnam.⁶

An attempt is made to strengthen the voluntary urinary sphincters by instructing the patient to start and stop the urinary stream several times during micturition. Ephedrine (25 mg.) is prescribed three times a day for its sympathicomimetic action. This drug contracts the internal sphincter and at the same time is a powerful depressant of vesical function.⁷

The material analyzed consisted of 175 consecutive cases seen at the Beth Israel Hospital Female Urologic Clinic from March, 1941, to March, 1947. The majority of the patients were intradepartmental referrals, presenting urologic symptoms, often after some form of surgery had been performed on the vaginal walls. Many of these patients presented cases of incontinence which had been treated surgically for the cure of this symptom. Some of the others had various types of vaginal surgery. Among these 175 cases, 82 patients presented themselves with the chief symptom of urinary incontinence, with or without other urologic complaints. The high incidence of incontinence in this series may appear unusual when compared to similar studies reported elsewhere. However, it must be kept in mind that this group was a hand-picked series selected for the analysis and treatment of urinary complaints usually in older women, often occurring after operations for cystocele.

Although urinary incontinence in the majority of women is due to injuries incurred during parturition, the symptoms often fail to make their appearance until after the menopause. Seventy-six per cent of the patients in this group fell into either the menopausal or postmenopausal decades. Of the 82 incontinent cases, 70, or 85 per cent, were between 41 and 70 years of age.

Cases were classified as to the degree of incontinence,⁸ as shown in Table I.

TABLE I

| | NUMBER OF PATIENTS |
|--|-----------------------|
| Mild incontinence occurs paroxysmally on stress following lifting, coughing, or sneezing | 50 |
| Moderate grade of incontinence occurs regularly following any form of exertion | 27 |
| Marked incontinence occurs on change of position | 4 |
| Complete incontinence is inability to retain urine in the bladder regardless of position | 1 |

The cases can be grouped further clinically as follows:

Group I. Cases of incontinence which had had no previous vaginal surgery.

Group II. Patients in whom incontinence first appeared after vaginal surgery.

NONOPERATIVE TREATMENT OF URINARY INCONTINENCE IN WOMEN*

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(From the Urologic Clinic of the Beth Israel Hospital)

INCONTINENCE may vary from mere dribbling on occasions to complete loss of urinary control at all times. Just as there is a variation in sensitivity to pain, so is there a difference in the reaction of individuals to loss of bladder control. "Stress incontinence"^{1, 2} indicates loss of urine under various circumstances related to effort on the part of the patient, such as lifting, coughing, sneezing, etc. It is these cases which are properly subjected to operative treatment; but clinically, true stress incontinence is difficult to differentiate from false incontinence caused by irritative lesions in the bladder or urethra.

One of the commonest causes of urinary complaints in the female, which may be present from early infancy throughout life, is a papillary posterior urethritis due to infection in the glands near the vesical orifice. Folsom⁴ believed that this infection may take place during the diaper stage of life. Infections of various types, ascending from the vulva and vagina, may create inflammatory lesions in the urethra and bladder. Among the etiologic agents, the trichomonas, Monilia, and many varieties of bacteria may cause irritative lesions resulting in false incontinence.

No satisfactory test has been devised to determine whether a patient has true or false incontinence. X-ray studies, cystometric readings, endoscopy, and cystoscopy have all proved of little value in differentiating true from false incontinence. A test commonly used to detect incontinence in women is performed by instilling 250 c.c. of saline into the bladder and having the patient cough or strain while in the lithotomy and erect positions. However, during this test the patient may voluntarily close her external sphincters and prevent leakage, while under ordinary conditions when she sneezes, lifts a heavy object or coughs, she is not on her guard to prevent bladder loss.³ For this reason, this test should not be used as a reliable index to determine incontinence.

At the present time the treatment of urinary incontinence in women is largely surgical, attempting by operative measures to restore damaged structure and function. Occasionally women who have had excellent technical operative repairs for supposed stress incontinence may remain incontinent because their loss of bladder control was never due to true "stress incontinence." Other patients, following operation for cystocele without incontinence, have developed incontinence after well-conceived and well-executed operative measures. The incontinence in many of the latter cases is believed to be due to irritative lesions in the bladder or urethra, or both, created by the operation; and thus should be classified as false incontinence. Sometimes true "stress incontinence" is present together with false incontinence.

*Read before the Section of Obstetrics and Gynecology on Oct. 28, 1947, at the Academy of Medicine.

4. This method may at times be used successfully in preventing unnecessary operations on patients with false incontinence, and in the salvage of patients suffering from incontinence unimproved by surgery; or following operations on the anterior vaginal wall.

5. Of 68 cases of urinary incontinence with adequate therapy and follow-up, 27 (or 40 per cent) were cured; 28 (or 41 per cent) were improved, while 13 (or 19 per cent) were not helped by this form of therapy.

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Group III. Cases following vaginal surgery who although preoperative incontinence had been noted, had had no specific operative procedure for its cure.

Group IV. Cases of incontinence who had had vaginal surgery for the cure of incontinence with failure.

TABLE II. DURATION OF THERAPY

| | |
|----------------|----------|
| 1 month | 22 cases |
| 2 to 3 months | 21 cases |
| 3 to 6 months | 14 cases |
| 6 to 18 months | 11 cases |
| Did not return | 68 cases |
| Total | 14 cases |
| | 82 cases |

The results of treatment are indicated in Table III.

TABLE III. ANALYSIS OF CASES

| | NUM- BER OF CASES | ANTERIOR VAGINAL WALL | | | RESULTS OF THERAPY | | | |
|---|-------------------------|-----------------------|----------------|-------------------------|--------------------|---------------|-------------|----------------------|
| | | ADE- QUATE | CYSTO- CELE | OVER- COR- RECTED | CURED | IM- PROVED | FAILURE | NOT RE- TURNED |
| Group I. No surgery | 30 | 11 | 19 | 0 | 9 | 12 | 5 | 4 |
| Group II. Postoperative incontinence | 14 | 8 | 4 | 2 | 3 | 4 | 4 | 3 |
| No preopera- tive inconti- nence | | | | | | | | |
| Group III. Untreated preoperative incontinence | 15 | 10 | 3 | 2 | 7 | 5 | 0 | 3 |
| Group IV. Incontinence not cured by surgery | 23 | 15 | 2 | 6 | 8 | 7 | 4 | 4 |
| Total | 82 | 44 | 28 | 10 | 27 (40%) | 28 (41%) | 13 (19%) | 14 |

Summary

1. False incontinence due to irritative lesions of the urethra, vesical neck, and bladder is frequently encountered in women. False incontinence is often confused by the doctor and patient and considered to be stress incontinence. The two conditions may co-exist.

2. No adequate tests have been described to differentiate these two types of incontinence. The so-called continence test cannot be used as a reliable index to measure incontinence.

3. It has been found that dilatation of the urethra, topical applications of silver nitrate, and the use of ephedrine will usually cure false incontinence. The method described may be used, therefore, as a therapeutic test to differentiate false from true stress incontinence prior to surgery.

from one piece of natural or synthetic latex, and is pliable enough to vary its contour, depending upon the pressure gradients upon it. The latex bag is made in only one size. It can be introduced readily through a cervix where only 2 cm. of dilatation exist. Quoting from Woodward,⁹ "When it (the bag) is placed in the uterus, the pressure upon its upper portion causes that portion within the cervix to expand and to exert outward pressure on the cervical ring in a much more positive manner than the non-elastic, wedge-shaped bag. For this reason, it is only rarely necessary to apply traction . . . When the bag is pushed out by pressure from above, the dilatation is greater than the circumference of the bag, because with each contraction of the uterus the bag is shortened and its circumference expanded."

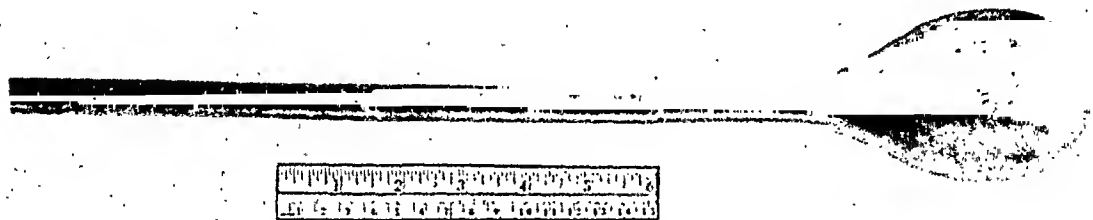


Fig. 1.

Method of Use

The bag is attached by a rubber tubing to a Kelly bottle and sterile water is allowed to run in until the bag is the desired size (usually holding 400 to 500 c.c.). All air is expelled from the bag and tubing. The water is allowed then to run back into the Kelly bottle, creating a vacuum in the bag and facilitating the folding. The collapsed bag is folded and grasped with a curved sponge stick and then is introduced by touch (or preferably by sight) through the cervical os.

When the bag is inside the os, the sponge stick is removed, the tubing unclamped, and the water slowly fills the bag. The neck of the bag is secured with a clamp, and the tubing is disconnected. This technique is preferred to that of filling the bag with a syringe because of its convenience, ease, and less chance for contamination.

Incidence

During the ten-year period included in this paper, there were 22,935 deliveries; in 244 cases the delivery was aided by a bag, giving an incidence of 1 per cent. (Table I.) This rate is higher than that reported elsewhere.^{1, 6, 11} The policy of conservative obstetrics has always been dominant in this hospital, and readily accounts for this high incidence. During the last four years, however, the use of the bag has decreased slightly because of the re-evaluation of its indications and the lack of good latex necessary to manufacture new bags.

TABLE I. INCIDENCE OF USE

| | |
|---|--------|
| Total deliveries (1938-1947 inclusive) | 22,935 |
| Delivered with bag | 244—1% |

THE HYDROSTATIC BAG IN OBSTETRICS*

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THE use of the hydrostatic bag in obstetrics has been a debatable point for many years. Opinions expressed in modern textbooks and recent literature lead one to believe that the bag is a relic of a past era, and has no place in modern obstetrics.^{1, 3} Others,^{2, 4-9} however, maintain that certain indications exist where it may be employed advantageously.

For this reason, it was deemed necessary to collect a series of cases in which the same elastic bag was used and the procedure did not vary. An attempt was made to scrutinize the indications, fetal and maternal mortality and morbidity, along with other complications inherent in the use of the bag. Based on these factors, certain conclusions regarding this controversial subject can be drawn.

Material

The material included in this paper was collected from the obstetric records of the Cincinnati General Hospital. It covered a ten-year period from 1938 to 1947, inclusive. The insertion of the bag and the ultimate delivery were performed by one of the members of the resident staff. Many of these patients were subjected to various vaginal or rectal examinations by members of the house staff and senior medical students for instructional purposes. Others were referred to this hospital following mismanaged labor in the home. Most of them had had no prenatal care. It was expected, therefore, that the maternal morbidity would be high.

Type of Hydrostatic Bag

According to Woodward and Gardner,⁹ the earliest bag to be used was a bladder type devised by Schnakenburg in 1831, which was discarded soon thereafter. This was replaced by Carl Braun's rubber balloon-shaped bag. De Ribes and Voorhees described the nonelastic bag, which became popular and is now employed in many hospitals in this country. The nonelastic bag, however, has several disadvantages. When distended with fluid, it acts as a driving wedge, and possesses no elasticity or adaptability. One often resorts to traction to force this unyielding mass through the cervix, frequently with resulting lacerations. Furthermore, different sizes must be used to effect adequate dilatation, necessitating longer time, more manipulation, and greater possibility of infection, trauma, and prolapse of cord.

In this department, the original Braun bag has been modified by technicians† in this city to eliminate all seams and rough edges. (Fig. 1.) It is molded

*Read before the Cincinnati Obstetric Society, Feb. 19, 1948.

†Present bag is made by Mr. Waldo Younkers following the specifications set forth by Dr. William P. Gillespie.

in utero when the diagnosis is made, and the cervix often is partially dilated, soft, and easily amenable to vaginal delivery. In the primipara with a long, hard, uneffaced cervix, the procedure of choice is cesarean section regardless of whether the infant is alive or dead. In abruptio placentae as well as in other types of hemorrhage, the membranes were ruptured artificially first, bringing about as much contraction of the uterus as possible, and the bag inserted intraovularly. It is necessary also to note exactly when the bag is expelled from the uterus in order to prevent the accumulation of blood behind it. As soon as the bag is found in the vagina, the patient should be prepared for immediate delivery.

The same criteria have been applied to partial separation of the placenta. Seven cases of this type having been treated with the bag, resulting in five living, one stillborn, and one nonviable infant. Other types of bleeding, listed in Table II, are of secondary importance and need no further discussion.

TABLE II. INDICATIONS FOR USE

| INDICATION | NO. OF CASES |
|---------------------------|--------------|
| 1. <i>Bleeding.</i> — | |
| A. Placenta Previa | 64 |
| Central | 12 |
| Partial | 29 |
| Marginal | 23 |
| B. Abruptio placentae | 23 |
| C. Partial separation | 7 |
| D. Late abortion | 4 |
| E. Circumvallate placenta | 2 |
| F. Low Implantation | 5 |
| G. Undetermined | 3 |
| Total | 108 |
| 2. <i>Dilatation.</i> — | |
| A. Prolonged labor | 54 |
| B. Breech | 19 |
| C. Transverse | 13 |
| D. Twins | 4 |
| E. Miscellaneous | 12 |
| Total | 102 |
| 3. <i>Toxemia.</i> — | |
| A. Pre-eclampsia | 20 |
| B. Eclampsia | 14 |
| Total | 34 |

(2) *Dilatation.*—In this group were included the patients in whom the bag was used to secure full cervical dilatation because of insufficient natural forces, or because of some abnormality in presentation. The presence of the bag in the lower segment and cervix initiated regular contractions, and dilatation proceeded rapidly. The bag was chosen only after elimination of cephalopelvic disproportion as an etiological factor. Accordingly, 54 cases classified as prolonged labor, due either to uterine inertia or cervical dystocia, were delivered after being aided by the elastic bag. (Table II.) Adequate cervical dilatation was successfully secured in all cases.

Breech, mostly footling variety, and transverse presentations constituted other indications. Reduction in fetal mortality was secured in the cases of transverse presentation treated by the use of the bag. The reason for this was that the bag not only secured cervical dilatation, but prevented rupture of the membranes and prolapse of the cord, thereby facilitating the performance of delivery by podalic version.

Indications

Accepting Webster's⁶ classification, we schematically divided the patients into three main groups for: (1) Bleeding, (2) aid in cervical dilatation, and (3) induction of labor in toxemia.

Fig. 2 shows the percentage of cases in each group.

INDICATIONS

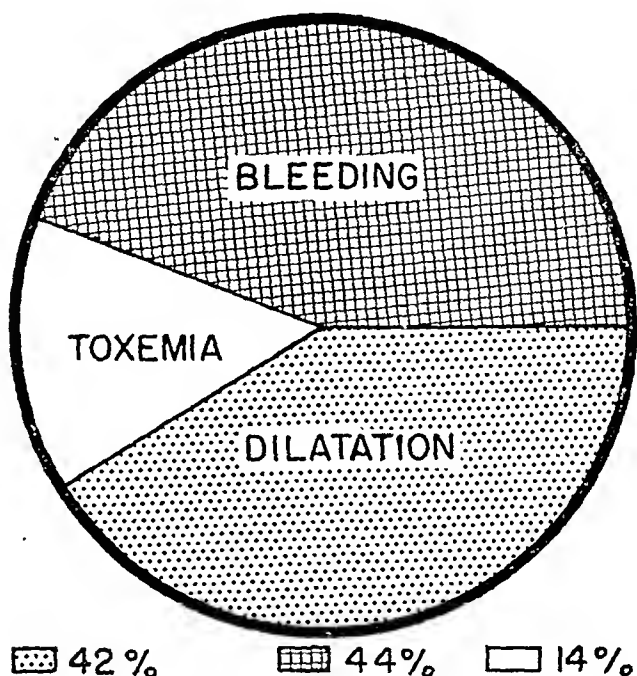


Fig. 2.

(1) Bleeding.—Many authors^{4, 6, 7} believe that placenta previa is the major indication for employment of the elastic bag. Table II reveals that this complication accounted for 64 cases. Of these, 12 were central placenta previa; 3 of them were treated by inserting the bag in the vagina in an attempt to control hemorrhage until the operating room could be prepared for cesarean section. In these 3 cases the infants survived, while 7 of the remaining 9 cases delivered vaginally resulted fatally for the infants. Therefore, we no longer advise the bag in the treatment of central placenta previa. The present trend of thought in this department is to limit the bag to partial placenta previa (with artificial rupture of the membranes) when the cervix is soft and partly dilated. The marginal type is treated most advantageously by rupture of the membranes alone, and, occasionally, by bag insertion.¹⁰ In the majority of cases of placenta previa, the infant is premature and can be delivered easily by the vaginal route, following control of hemorrhage and cervical dilatation.

Abruptio placentae was the second indication among the bleeding patients. The bag was used 23 times for this complication, and only three live infants were delivered. The majority had no fetal heartbeat on admission.

Abruptio placentae in the multipara is still listed among our primary indications. This is justified by the fact that the infant has usually expired

(Table V.) Fig. 3 shows the incidence of morbidity in each group of cases. In the bleeding group, the morbidity was higher because some of the patients were in poor general condition upon arrival at the hospital, due to extreme blood loss. Recently, we have been able to lower the maternal morbidity considerably with prophylactic sulfonamides, and parenteral or vaginal penicillin.¹²

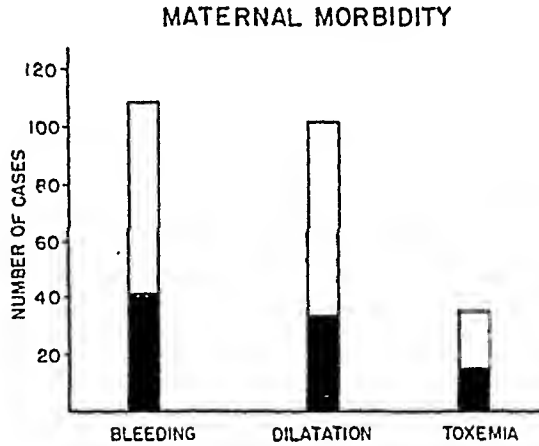


Fig. 3.

TABLE V. COMPLICATIONS

| | CASES | PER CENT OF TOTAL |
|---------------------|-------|-------------------|
| Infection | 86 | 35 |
| Cervical laceration | 9 | 3.7 |
| Prolapsed cord | 24 | 9.8 |

Nine cases were found to have cervical lacerations. The trauma, however, was possibly produced by the internal podalic version which frequently followed the extrusion of the bag.

Prolapse of the cord occurred in 24 cases resulting in six infant deaths and three nonviable stillborns. These figures might possibly be reduced by more careful auscultation of the fetal heart immediately after insertion of the bag, and again after its expulsion into the vagina.

Displacement of the fetal position is attributed by several authors to the use of the bag. This complication, however, was observed only in a few cases, and did not cause serious difficulty in the outcome of the delivery.

Fetal Mortality

The gross fetal mortality for the entire series was 43 per cent and the corrected 25 per cent. (Table VI.)

Fig. 4 shows the corrected fetal mortality in each group. These figures were corrected by excluding congenital abnormalities incompatible with life, and macerated, nonviable fetuses. Prematurity was not considered as a correction factor. For the bleeding cases, the corrected fetal mortality dropped from 57 to 27 per cent; for the dilatation group, from 27 to 20 per cent; and for the toxie group, from 48 to 30 per cent. Our gross fetal mortality was less than that reported by Webster,⁶ but our corrected mortality was apparently higher, because of a difference in the correction factor.

Other cases (miscellaneous) of premature rupture of the membranes, prolapsed cord, twins, brow presentation, face presentation, anencephalics, also were treated with the bag.

(3) Toxemia.—It is well recognized that the best approach in the treatment of patients with toxemia is along conservative lines. The policy of this department has been to induce labor in eclamptics only after the convulsive stage has been controlled, and the patient is in good general condition. Medical induction with stripping of the membranes is attempted first. Where this fails, and when the condition of the cervix permits, a bag is inserted extraovularly, and delivery is effected by the vaginal route. In rare cases, because of disproportion, or the condition of the cervix, cesarean section is performed.

Induction of labor was secured by the bag in 20 pre-eclamptic and 14 eclamptic patients. (Table II.) Eighteen living babies were delivered, giving a gross fetal mortality of 48 per cent and corrected of 30 per cent.

Type of Delivery

In this series there were nine sets of twins, giving a total of 253 infants. Spontaneous and podalic version were the predominant types of delivery. (Table III.) Five patients were delivered by cesarean section after the insertion of the bag. As stated before, in three cases of central placenta previa the bag was used in the vagina to control hemorrhage. In the remaining two, cephalopelvic disproportion was not detected, and extraperitoneal cesarean section was performed after an unsuccessful attempt to perform vaginal delivery.

TABLE III. TYPE OF DELIVERY

| | NO. OF CASES | SPONTANEOUS | PODALIC VERSION | FORCEPS | BREECH | CESAREAN SECTION |
|------------|-----------------|-------------|--------------------|---------|--------|---------------------|
| Bleeding | 108 | 54 | 34 | 7 | 10 | 3 |
| Dilatation | 102 | 18 | 28 | 27 | 27 | 2 |
| Toxemia | 34 | 15 | 8 | 6 | 5 | 0 |
| Total | 244 | 87 | 70 | 40 | 42 | 5 |

Parity

Table IV shows that, in the bleeding cases, 85 per cent were multiparas, mainly because placenta previa was more common in the multiparas, and most of the primiparas were treated by cesarean section. Of the total, 66 per cent were multiparas.

TABLE IV. PARITY

| INDICATION | PRIMIPARAS | MULTIPARAS |
|------------|------------|------------|
| Bleeding | 16 | 92 |
| Dilatation | 52 | 50 |
| Toxemia | 15 | 19 |

Complications

Puerperal infection frequently follows the use of the hydrostatic bag.^{2, 3, 11} Many authors have decided to eliminate its employment chiefly because of this danger. With this in mind, careful study was made of all cases which presented a temperature of 100.4° F. on any two days, exclusive of the first twenty-four hours post partum. Eighty-six patients were classified as infected.

The first case was a 42-year-old multipara, admitted to the hospital because of ante-partum eclampsia, bronchial asthma, and heart failure. She was delivered by an internal podalic version and breech extraction following bag induction. She developed a subphrenic abscess, and died 35 days after admission.

The second case was a 35-year-old, colored multipara admitted in shock with a diagnosis of placenta previa marginalis. She was delivered by internal podalic version after insertion of the bag. Death was due to uncontrolled hemorrhage, and autopsy revealed a laceration of the lower uterine segment, which was not recognized and possibly was due to the mode of delivery.

The third case was a 32-year-old, white multipara admitted in severe shock, with a diagnosis of premature separation of a low implanted placenta. Delivery was by podalic version and breech extraction after insertion of the bag. She died of infection a month later.

The fourth case was a 32-year-old, white multipara who presented the findings of the dystocia dystrophy syndrome with primary uterine inertia. Dilatation was secured with the bag, and she was delivered by internal podalic version and breech extraction. Severe post-partum hemorrhage ensued, and a delayed hysterectomy was performed, but the patient died a few hours later.

In all of the aforementioned cases, death was considered preventable.

Discussion

An analysis of the figures reported in this paper leads one to believe that there is still a place for the hydrostatic bag in obstetrics. The success of this procedure, however, depends on several factors: the choice of the type of bag to be used, the technique of its employment, the judicious selection of cases, and the close observation of the patient during labor and delivery. The selection of the correct bag and the type of patient are of paramount importance.

The fetal mortality in this series could not be compared with that reported for cesarean section since many of these patients were not suitable for abdominal delivery.

The maternal morbidity could be reduced by regular use of antibiotic drugs. Furthermore, the use of the bag in such cases was justified by the large incidence of prematurity and multiparity, and by the poor general condition of the patients.

From the available data, the following indications for the use of the hydrostatic bag can be selected:

1. Placenta previa partialis, and occasionally marginalis.
2. Abruptio placentae when the infant has already expired, and the cervix is somewhat dilated and soft.
3. Transverse presentations in the multipara when the cervix is amenable.
4. Breech presentations, particularly footling variety in the primipara, or in the multipara with partially obliterated cervix, and when there has been premature rupture of the membranes and failure to progress.
5. Induction of labor in the toxemic patient when the cervix is amenable, and more conservative methods have failed.
6. Uterine inertia in the absence of disproportion, when there is no evidence of intrauterine infection.

TABLE VI. FETAL MORTALITY

| | NO. OF CASES | STILLBORN | NEONATAL DEATHS | TOTAL | GROSS MORTALITY RATE (PER CENT) |
|------------|-----------------|-----------|--------------------|-------|---------------------------------------|
| Dilatation | 108 | 54 | 7 | 61 | 57 |
| Bleeding | 102 | 22 | 6 | 28 | 27 |
| Toxemia | 34 | 12 | 4 | 16 | 48 |
| Total | 244 | 88 | 17 | 105 | 43 |

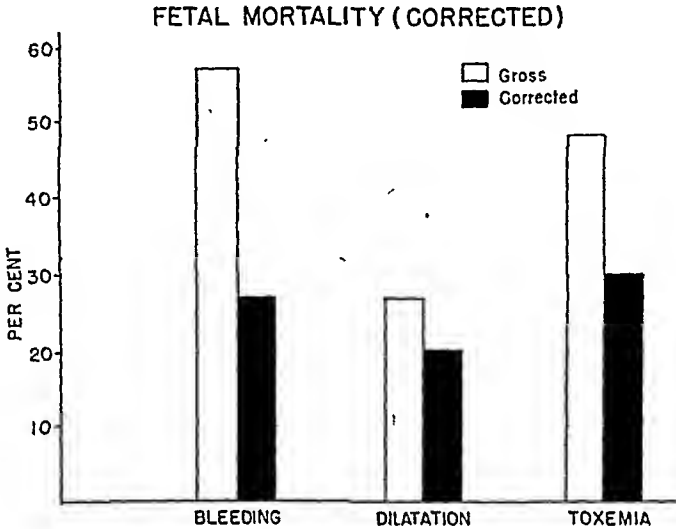


Fig. 4.

Prematurity

Eighty-seven infants were premature, and 52 of these were either stillborn, or died neonatally. (Table VII.) The highest incidence of prematurity was observed in the bleeding cases. These figures emphasize the fact that the use of the bag is a wise procedure in a patient with a premature infant having only a minimal chance of survival. Premature babies were classified according to their weight (less than 2,500 Gm.), and according to the length of gestation.

TABLE VII. PREMATURETY

| | CASES | PREMATURES | DEATHS | PREMATURE MORTALITY RATES (PER CENT) |
|------------|-------|------------|--------|--|
| Bleeding | 108 | 54 | 38 | 70 |
| Dilatation | 102 | 13 | 7 | 53 |
| Toxemia | 34 | 20 | 7 | 35 |
| Total | 244 | 87 | 52 | 60 |

Maternal Mortality

There were four maternal deaths in this series. In none of these, however, could a definite relationship between the cause of death and the use of the bag be demonstrated.

CHONDRODYSTROPHY FETALIS

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INTEREST in the subject of chondrodystrophic dwarfism was given added impetus at The Chicago Lying-in Hospital, when, on April 22, 1947, a chondrodystrophic infant was delivered by cesarean section. Both parents of this baby were typical chondrodystrophic dwarfs. Although the incidence of infants born with this developmental defect is not sufficiently rare to warrant comment, the fact that both parents also presented this form of dwarfism makes the case worthy of report and some discussion. The very extensive work of Rischbieth and Barrington¹ (1912) lists only two instances in which a baby and both parents were chondrodystrophic. A partial review of the literature from 1901 to 1942 discloses no similar cases. A newspaper item published in Denver, Colorado, in 1943, stated that a dwarf baby had been born by cesarean section to dwarf parents, but we have been unable to verify this report. Both parents seem to have been dwarfs, but whether they were chondrodystrophic is not certain.

Our case report is as follows:

Mrs. J. M., a 28-year-old white, primigravid, married, chondrodystrophic woman, first reported to The Chicago Lying-in Outpatient Department on November 29, 1946, for prenatal care. She was escorted by her husband, who was also a typical chondrodystrophic dwarf. Her past medical history was not noteworthy except that she had had defective skeletal development since birth. She had attended public schools, where her progress had been average. The patient's father and mother are living, well and normal. She has five sisters and one brother, all living, well and normal. No dwarfism was found when her pedigree was traced through four generations. The patient's husband was able to establish a pedigree through three generations in which there was no dwarfism. His father, mother, and three brothers are all living, well and normal. Each of his brothers is married and has two, three, and three normal children, respectively. Mrs. J. M.'s obstetric history was not unusual. Her menses appeared at the age of 15 years, the cycle was twenty-eight days, and the duration was two days. Her last menstrual period was August 20, 1946, and it was normal. The estimated date of confinement was May 27, 1947. Physical examination showed the patient to be in good health. All the findings characteristic of chondrodystrophy were present. There was no evidence of rickets. Her height was 116 cm., and she weighed 33.7 kg. The pelvic examination was recorded as follows: external genitalia normal; introitus nulliparous; vagina normal; the cervix was above the pelvic inlet and could not be palpated because of the pelvic deformity; the sacrum was displaced anteriorly so as to lie almost against the symphysis; the uterus, palpated abdominally, was enlarged to the size compatible with twelve weeks' gestation; the adnexae could barely be reached through the lateral portions of the pelvis and no abnormalities could be made out; a moderate lumbar lordosis was present. The pelvic measurements were: intercrural 21 cm.; interspinous 20 cm.; bitrochanteric 27 cm.; external conjugate 13 cm.; bischial 6 cm.; the pubic arch was narrow and the angle at the symphysis was acute; the conjugata vera was no more than 2 cm. The patient was given routine prenatal care, and it was anticipated that pregnancy would be terminated by laparotrachelotomy at approximately the 38th week of gestation.

The prenatal course was uneventful until April 22, 1947, at which time active labor began and the membranes ruptured spontaneously. A cesarean section was performed immediately, using $\frac{1}{2}$ per cent Novocain local anesthesia. A living, female, premature chon-

Summary

Two hundred and forty-four patients delivered with the use of a hydrostatic bag were studied.

A type of bag made of latex, the technique, and the advantages of its use were described.

Control of bleeding, induction of labor, and securing cervical dilatation were the major indications for the use of the bag.

The gross fetal mortality was 43 per cent, and the corrected (including prematures) 25 per cent.

The maternal death rate in this series was 1.7 per cent.

Infection and prolapse of cord were the major complications.

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was recognized by Rischbieth and Barrington in 1912, no chondrodystrophic woman can deliver a viable baby vaginally because of the pelvic deformity constantly associated with this condition.

In spite of the great interest in dwarfism, as evidenced by the accumulated historical records, literary classics, objects of art, and scientific reports, the etiology of chondrodystrophic dwarfism remains vague and subject to debate. The malformation has been attributed to almost every possible cause. At the present time it is generally believed that heredity is an important factor and that mutations producing this abnormality and subsequently capable of being inherited appear with a fair degree of frequency. It is not clear whether the hereditary effect is transmitted through the endocrine system or through the factors concerned with skeletal development. That the hereditary aspect of dwarfism is not a recent idea is evidenced by the attempts of Catherine de Medici and others to produce a dwarf race by intermarriage. Study of pedigrees in which chondrodystrophy occurs leaves no doubt that heredity is involved. Geneticists in general are of the opinion that the inheritance is transmitted through simple Mendelian factors. The failure of dwarfism to appear in all generations of a pedigree is explained by the so-called "skipping mechanism" due to a lack of "penetrance" of the genes.²

Related to the hereditary aspects of chondrodystrophy is the high death rate of affected babies. The high incidence of intrauterine death at about the eighth month of gestation is recognized, and the prognosis for those babies born alive must always be guarded since many die during the first year of life. No satisfactory explanation has been advanced for this high mortality, although it has been suggested that, in many instances, early death is due to a premature synostosis of the four segments of the occipital bone, resulting in a compression of the growing spine and brain stem at the foramen magnum. The "lethal effect" of homozygous inheritance factors has been suggested as a cause of early death and has been supported by proof of this phenomenon in experimentation with chondrodystrophic animals.

Since 1931, during the course of over 48,000 deliveries, four other chondrodystrophic infants have been born at The Chicago Lying-in Hospital. Two were delivered by cesarean section, one by version and extraction, and one by midforceps. None of these babies survived; all were stillborn or failed to live beyond the early neonatal period. Six other chondrodystrophic infants were received at this hospital for autopsy from other Chicago sources. The parents of all ten infants were without evidence of chondrodystrophy and in no instance could a history of dwarfism in other members of the family be obtained.

During the period of Mrs. J. M.'s hospitalization, it was possible to contact eleven other chondrodystrophic dwarfs in the Chicago area. These people were all willing to discuss their deformity. The following information and opinions were obtained from them:

1. The estimated number of chondrodystrophic dwarfs in the Chicago area is forty.
2. The estimated number of chondrodystrophic dwarfs in the United States is approximately 2,000. (No accurate census is available.)
3. The parents of the 11 individuals interviewed were normal, and there was no other dwarfism in their families.
4. The individuals contacted knew of the following families in which dwarfism is present:
 - a. Four families in which the father is chondrodystrophic and the mother is normal. The children of these parents are all normal.
 - b. One family in which husband, wife and three children are normal and three children are chondrodystrophic.
 - c. One family in which both husband and wife are normal but all of their five children are chondrodystrophic.
5. Very few chondrodystrophic dwarfs marry. Those who do usually marry normal individuals. Marriages in which husband and wife are both chondrodystrophic are exceedingly rare.

drodystrophic infant was delivered. She cried spontaneously and appeared to be in good condition. The mother's postoperative course was normal and she was discharged on the twelfth hospital day.

The infant at birth weighed 2,310 Gm., measured 43 cm. in total length, and was of 34 weeks' menstrual age. Physical examination revealed the following characteristic findings of chondrodystrophy: mild macrocephaly, prominent frontal and parietal bosses, saddle-pug nose, abnormal shortness of the extremities associated with exaggerated curvature of the long bones and overgrowth of soft tissue, trident-shaped hands, and normal length of the body trunk. The infant's hospital course was not unusual except that weight gain was slow. The baby was discharged on the twenty-first hospital day weighing 2,510 Gm. (Fig. 1). Subsequent examination on July 3, 1947, revealed a well, vigorous infant who was gaining weight normally.



Fig. 1.

Discussion

The management of this case presents no obstetric problem. The indication for cesarean section in all chondrodystrophic dwarfs is clear cut and without alternative. As

TORSION OF FALLOPIAN TUBE

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TORSION of a tube is not a rare condition, but torsion of a previously undiseased tube is. Regad,¹ in discussing the relative frequency of torsion of the tube based on 201 cases, found torsion of the undiseased tube in 24 per cent of the cases. However, histologic examination was done in only 8 per cent of these. It is my belief that, had it been done in more of these, there would have been found a smaller percentage of previously undiseased tubes. He found torsion of a hydrosalpinx in 18 per cent, torsion in hernial sac in 14 per cent, torsion in salpingitis, ectopic, or tumor in 13.5 per cent; torsion in the course of pregnancy in 12 per cent, with various other conditions making up the additional percentage. Anderson² reports the torsion of an apparently normal ovary and spontaneous amputation of the tube occurring in a 12-year-old girl with a one-day history of pain. In this case the tube was amputated 1.5 cm. from the cornu. Kaminester³ reported the case of a 24-year-old patient; gravida i, para i, with a twist due to a small parovarian cyst. Goldberg and Olm⁴ reported a case due to twisted hydrosalpinx. Savage⁵ reported a case of a twisted hematosalpinx complicating pregnancy. That case was the fifteenth reported up to that time.

The case to be reported here is that of a torsion of a previously undiseased tube.

Case History

Mrs. J. M., a 37-year-old gravida ii, para ii, was admitted to the South Nassau Communities Hospital complaining of pain in the right lower quadrant of three days' duration. Patient's periods began at 15½ years and were always regular until last pregnancy. Since then she has on several occasions been as much as two days late. Patient had a normal period in April, 1947. Her May period, however, was five days late, occurring on May 30, and being normal in amount and duration. The evening of June 15, she developed pain in lower abdomen particularly on the right side. The pain became severe during the night. Findings were: normal pulse and temperature, a soft abdomen, with slight tenderness in the right lower quadrant. A white blood cell count and differential count done the next day were normal. Patient, however, continued to have intermittent pain in the lower abdomen on June 16 and 17. Early on the morning of the 18th, she had more severe pain and while in the bathroom actually fainted.

At this time she was seen in consultation, and the significant findings were a temperature of 100° F., pulse 100. The abdomen showed definite spasm and rigidity of the lower quadrants, particularly on the right side. There was direct tenderness in the right lower quadrant but even more marked rebound tenderness. External genitals were normal; cervix not particularly soft; fundus of normal size and firm. In the right fornix was a mass measuring about 6 by 8 cm. This was exquisitely tender and felt cystic. There was no blood on the examining finger. With these findings, patient was admitted to hospital with a diagnosis of either a right ectopic pregnancy, with tubal abortion, or, a twisted right ovarian cyst.

Laboratory Data: The red blood count was 4.1 million, hemoglobin 82 per cent, white blood count 9,000 with 80 per cent polymorphonuclear leucocytes. The urine was negative.

Patient was operated upon shortly after admission to the hospital. Upon opening the peritoneal cavity, it was noted that there was an increased amount of fluid, culture of which was taken, and subsequently found to be sterile. There was no blood in the peritoneal cavity. The only pathologic finding was that in the right tube. This showed two complete twists upon itself at the midportion. The proximal portion of the tube appeared normal. The distal half, however, was much dilated measuring 6 by 8 cm. The fimbriated end was closed. The dilated portion of the tube was tense, cystic, and showed bluish-red discoloration. A right salpingectomy was done.

Conclusions

1. Two instances have been found in the literature in which father, mother and child are chondrodystrophic dwarfs. The present report brings the total to three.
2. Cesarean section is always indicated for the delivery of a pregnant chondrodystrophic woman.
3. Prognosis for survival of chondrodystrophic infants should be guarded.
4. Chondrodystrophic children, for the most part, appear in families in which both father and mother are normal.
5. Chondrodystrophy seems to be inherited as a simple, dominant, Mendelian character complicated by:
 - a. Mutations which occur more frequently than has been generally appreciated.
 - b. "Skipping phenomenon."

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USE OF ESTINYL IN TREATMENT OF MISSED ABORTION*

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WHEN a growing fetus dies, it becomes in effect an intrauterine foreign body, which is usually expelled within a short time thereafter. Occasionally the entire dead material is retained within the uterine cavity for long periods before expulsion. There have been reports of instances where this situation continued for almost a year. The condition of dead and completely retained fetal mass has been named "missed abortion."

The evacuation of the products of conception in cases of missed abortion has long been a problem. In many instances the uterus seems to lack its normal capacity for contraction, and the emptying of the uterine contents is delayed until an operative procedure is performed for that purpose. Any agent that increases uterine irritability and contractility is therefore of distinct advantage. The use of estrogens which might increase uterine response would therefore seem rational under these circumstances.

By replacing the hydrogen at carbon atom 17 in alpha-estradiol with the ethinyl radical, a remarkable increase in effectiveness results. The product thus produced is ethinyl estradiol, hereinafter referred to as Estinyl. On a weight basis, Estinyl is from seven to seventy-eight times as active as other oral estrogens available today. Absorption is virtually complete in the gastrointestinal tract, and the ethinyl radical prevents inactivation of the estrogen by the liver. In regard to toxicity, 10 to 20 per cent of all nonpregnant patients experience gastrointestinal and other symptoms. The complaints referred to the digestive system are nausea and, more uncommonly, vomiting, diarrhea, and abdominal pain. Vertigo and headache have been reported. In pregnant patients, we have seen no untoward effects, though occasionally the tablets of Estinyl are excreted in the stool within half an hour or an hour after ingestion, intact and undigested.

Six cases of missed abortion are described which were treated by the administration of large doses of Estinyl with favorable results.

CASE 1.—D. C., aged 29 years, was admitted to the hospital on Sept. 24, 1945, because of vaginal bleeding of four days' duration. She had had two previous pregnancies, both full term, with spontaneous deliveries. Her last menstrual period was March 10, and the expected date of confinement was December 17. The patient stated that her abdomen seemed larger three months prior to admission than at the present time. On September 25, colostrum could be expressed from the breasts, but no milk. Abdominal examination revealed a rounded mass reaching to the umbilicus, about the size of four and one-half to five months' gestation. This ovoid swelling was definitely the uterus, as contractions and relaxations could be palpated. No fetal heart or movements were heard; there was no choe fetale. On vaginal examination, the cervix was soft with the external os open, but the internal os was closed and firm. A diagnosis of missed abortion was made. The Asehheim-Zondek test was negative of September 28. Radiologic examination of the abdomen revealed a pregnancy of about four and one-half months.

*We wish to thank the Schering Corporation for their generous supplies of Estinyl which made our study possible.

Pathologic Report.—Specimen consists of a tube, the proximal portion of which appears normal. The distal half is dilated, measuring 6 by 8 cm. The fimbriated end is closed. Section of the dilated portion of the tube reveals the presence of serosanguineous fluid. There is also some clotted blood present in the lumen and wall of the tube.

Diagnosis.—Twisted hematosalpinx.

Patient had an uneventful convalescence. The wound healed by primary union and the patient was discharged on the eighth postoperative day.

Comment

The case presented is one of torsion in a previously undiseased tube. This is corroborated by the finding of normal tubal lining and diameter in the portion of the tube proximal to the twist. The normal appearance of the other tube, plus the fact that the patient has two young children, likewise point to a conclusion that the tube was normal prior to the present episode. The exact frequency of occurrence of this condition in a nondiseased tube is difficult to determine because the pathologic examination is frequently inaccurate, the marked necrosis usually present obscuring the rest of the picture.

Blum and Sayre,⁶ in their article, review the various theories as to the possible mechanism of this condition. Of the various theories postulated, the following impressed me as being the most likely:

1. Anatomic theory, which states that malformations in the mesosalpinx or the tube favor torsion, e.g., long mesosalpinx, hydatids of Morgagni, persistence of the spiral winding normally present in the tube of the fetus.
2. Physiologic theory that a disturbance of the regular peristaltic movements of the tube, such as spasm, may give this condition.
3. Hemodynamic. The veins of the mesosalpinx are longer and more flexible than the arteries, and, in case of venous congestion, they assume a spiral course which favors torsion.
4. Sellheim's theory that sudden changes or stoppage of body movement may give rise to torsion.

The reason for the occurrence of this condition in the present case must remain unknown. There was nothing in the patient's previous history or in the operative findings to account for the occurrence of this condition.

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been made at five months, and confirmed on admission by x-ray. No labor pains occurred during five days, and 0.3 mg. Estinyl was ordered every two hours. The patient went into active labor after nine doses of Estinyl, the total dose being 2.7 mg. A macerated still-born fetus was delivered after two and one-half hours.

CASE 6.—B. S., aged 28 years, was admitted with a diagnosis of missed abortion. Her last menstrual period had taken place eight months previously, and no fetal movements had been felt since five and one-half months. No fetal heart was audible. Estinyl 0.3 mg. was administered every two hours for 41 doses, total amount being 12.3 milligrams. The patient did not go into labor, even though the Estinyl had been given for seventy-two hours, and Methergine one minim was given every thirty minutes, for three doses, producing strong tetanic uterine contractions, which lasted several minutes. The drug was stopped and the pains subsided. Methergine was again started, and strong contractions, though not tetanic, were elicited. The patient went into good labor and was delivered of a macerated fetus, the size of a five months' pregnancy. The use of Methergine is still under study by us. It is our belief that the Estinyl sensitized the uterus to the action of Methergine, resulting in the tetanic contractions.

Conclusions

Evacuation of the products of conception in cases of missed abortion was attempted by the administration of Estinyl. Results were generally very good, in five of six cases so treated. The dosage used was usually 0.3 mg. every two hours for a period of seventy-two hours if necessary. There were no untoward effects.

Since treatment of these cases, larger doses of Estinyl have become available to us for research. An article by us, on the induction of labor at term by the administration of Estinyl, is now in print. In those studies, it became apparent that larger, much larger, doses of Estinyl could and should be used; and it is now our practice to use as much as 1 mg. per dose, every hour. We feel that a result should be expected within, or at approximately, seventy-two hours, and that the medication should be continued for that period if necessary.

Our studies and results with Estinyl indicate that it is a potent estrogen, capable of initiating and maintaining labor contractions in the pregnant uterus. It is of considerable value in the treatment of missed abortion.

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969 PARK AVENUE

On September 29 at 9:00 A.M., 0.3 mg. of Estinyl was administered by mouth. Uterine cramps began three hours later, and the medication was continued at four-hour intervals. After 0.9 mg. of Estinyl had been given, good labor began. The membranes ruptured at 8:15 P.M., and a spontaneous delivery of a macerated four months fetus was accomplished. The placenta was expressed but it was not entirely intact, and digital curettage of the uterine cavity was performed. A small amount of placenta was obtained thereby. The postpartum course was uneventful, and the patient was discharged on Oct. 6, 1945.

CASE 2.—H. L., aged 32 years, was admitted on Sept. 20, 1945. She had had one previous pregnancy which was terminated by a low forceps delivery at full term. Her last menstrual period was April 19, and the expected date of confinement was January 26. On July 18 a third degree retroversion of the uterus was corrected by bimanual manipulation. On August 26 vaginal staining began and continued intermittently until the time of admission to the hospital. At no time was bleeding excessive, and there were intervals of several days to a week without any stain of bleeding. On August 30 the uterus was the size of a three and one-half months' gestation. On September 10 the Aschheim-Zondek test was positive. On September 19 a vaginal examination was performed because the uterus could no longer be palpated above the symphysis. The uterus was now the size of a ten weeks' gestation, soft and doughy in consistency. There was a slight bloody discharge. The diagnosis of missed abortion was made.

On September 20 at 9:00 A.M., 0.3 mg. of Estinyl was administered by mouth, and repeated every four hours until 0.9 mg. had been taken by the patient. Uterine contractions began soon after the third dose when the patient went into active labor. Within four hours spontaneous delivery of an abnormal ten weeks fetus occurred. The baby showed webbing with lack of development of the fingers and toes. The placenta was expressed, but this was not complete. A curettage was necessary to remove the remaining secundines. The placenta was thin and poorly nourished. Her postoperative course was uneventful, and the patient was discharged on September 23. On October 17 vaginal examination revealed the cervix closed and normal. The uterus was retroverted and slightly smaller than normal.

CASE 3.—B. L., aged 24 years, had her last menstrual period on March 6; this was her first pregnancy. She began to bleed on May 21, and a diagnosis of threatened abortion was made, and hormone therapy begun. The patient was examined on June 6, and the uterus found to be the size of a seven weeks' gestation. A diagnosis of missed abortion was made, and Estinyl 0.3 mg. was administered by mouth every two hours. After four doses—a total of 1.2 mg.—the patient expelled the complete sac, containing the placenta. No fetus was found. Her postpartum course was uneventful. The patient was checked over six months later as to capabilities for carrying a pregnancy to successful termination; endometrial biopsy showed a very poor progestational phase premenstrually. This patient is now just over three months pregnant, and on therapy outlined in a previous paper. This young woman is one of three married sisters, of whom one has two children, and the other miscarried twice, finally being carried to term with the third pregnancy on considerable hormone therapy.

CASE 4.—Mrs. T. was admitted to the hospital with a diagnosis of missed abortion. The last menstrual period had occurred six months previously. The uterus was the size of a four months' pregnancy. No fetal movements were heard, and the fetal heart was absent. Estinyl 0.3 mg. was given every two hours for six doses per day, over a period of four days, the total amount of Estinyl being 3.0 mg. On the fourth day, the patient went into good labor, and delivered spontaneously a complete sac, with macerated fetus and placenta; the fetus had three loops of cord wound tightly around the neck.

CASE 5.—R. S., aged 22 years, was admitted to the hospital on Oct. 15, 1946. This was her third pregnancy, the two previous being entirely normal. The last menstrual period was March 24, 1946. No fetal heart had been heard, and a diagnosis of fetal death had



Fig. 1.

Fig. 1.—Seven-month conjoined males. Note ruptured abdomen of fetus Two.
Fig. 2.—Radio-gram of twins.

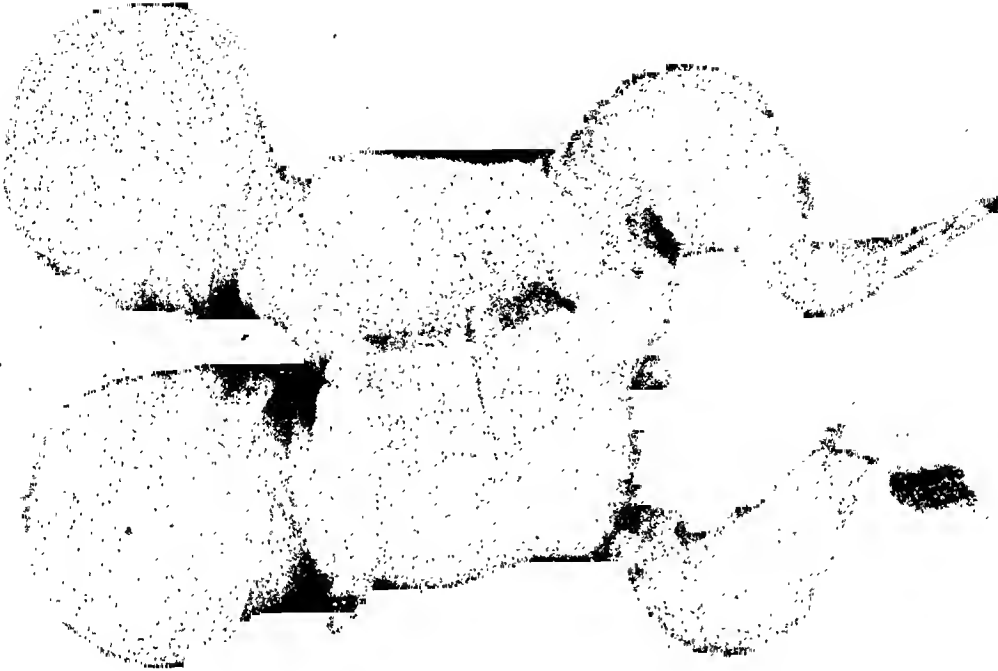


Fig. 2.

CONJOINED FETUSES (THORACOPAGUS) IN A DIZYGOTIC TRIPLET PREGNANCY

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(From the Department of Micro-anatomy College of Medical Evangelists)

MULTIPLE births, especially those involving more than two off-spring, never fail to arouse considerable interest. If some unusual feature accompanies the multiple births, interest is correspondingly increased.

The present case consisted of a female and two conjoined (thoracopagus) males. This seems to be the first case on record in which conjoined males have complicated a triplet pregnancy.

A noteworthy distinction of these conjoined fetuses is that the umbilical cord contained blood vessels normal for a single individual, i.e., two arteries and a vein. Messenger and Shryock reported a similar case from our own laboratory a few years previously, but their specimen had two arteries and two veins, one of each going to each twin. Shaw, Brumbaugh, and Novoy reported conjoined twins with six blood vessels in the umbilical cord which was a matter of simple duplication.

Clinical History and Delivery.—The mother was a primipara, twenty-three years of age. The father was twenty. There was no history of multiple births in either family. Wassermann reports were negative at the time of the marriage in August, 1945. The last menstruation was slight, lasting for but one and one-half days, and began Dec. 26, 1945.

The mother appeared to be in excellent health. There was no history of illness or injury during pregnancy. There was no evidence of vitamin or nutritional deficiency. There was no history of alcoholism, exposure to radiations, or the use of chemical douches or contraceptives. The mother worked until two weeks before the time of delivery. Her gain in weight was from 140 to 169 pounds.

The mother had been employed at the Corona Hospital, Corona, Calif. Delivery took place in this hospital. The first stage of labor began at 10:00 A.M., July 15. The membranes ruptured at 2:18 A.M., July 16. A female was born at 2:28. Birth was described as "easy," the child having "shot out like a cannon ball."

After this, the cord was clamped on the placenta side, there being no effort made to express the placenta as it was evident that another fetus was in the uterus. All pains ceased. At 4:00 A.M., pains began again but were very mild. One-half c.c. of Pituitrin was given. At 4:05, three feet, two rights and a left, appeared at the vulva. Examination was made to determine to which individual the right and left ones belonged. Attempts were made to reintroduce the other right one into the uterus. Traction was made on the left and right feet of one individual until they protruded outside the birth canal. The reintroduction of the foot and leg of the other individual into the uterus was unsuccessful. Further traction on the partially born individual was likewise unsuccessful. At this time, evidences of viability ceased. After consultation it was decided to extract first one and then the other. All attempts to do this were unsuccessful. Traction was increased to maximum until the abdominal wall of one individual ruptured. The twins were finally born en masse at 5:40 A.M.

Cervical and peritoneal repairs were made and the mother made an uneventful recovery.

The female, born first, was placed in an incubator but died at 1:46 P.M., July 16. Her weight was 3 pounds, 1 ounce. The combined weight of the twins was 5 pounds, 8 ounces. Crown-heel length indicated an approximate age of seven months.

Unfortunately, the fetal membranes were not preserved, but the attending physician had observed that there were two placentas, two umbilical cords, two amnions, and two chorions. One of each of these belonged to the female and the other to the conjoined males.

Both atria emptied into the large ventricle. Ascending aortae arose from opposite sides of this ventricle, one to each fetus. A patent interventricular foramen joined the two ventricles. A pulmonary artery ran from the small ventricle and branched presently to the lungs of each fetus. A ductus arteriosus joined the pulmonary artery in fetus Two with its aorta. Both atria received pulmonary veins and superior venae cavae in addition to the inferior ones mentioned previously.

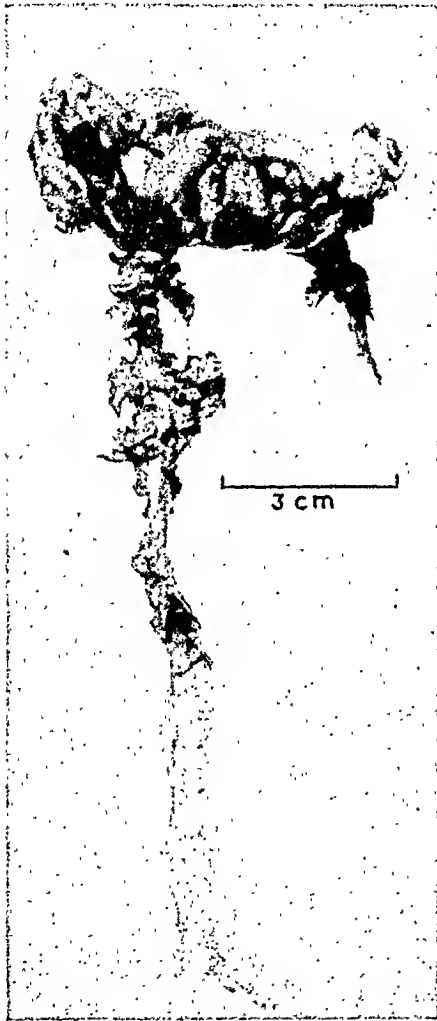


Fig. 4.

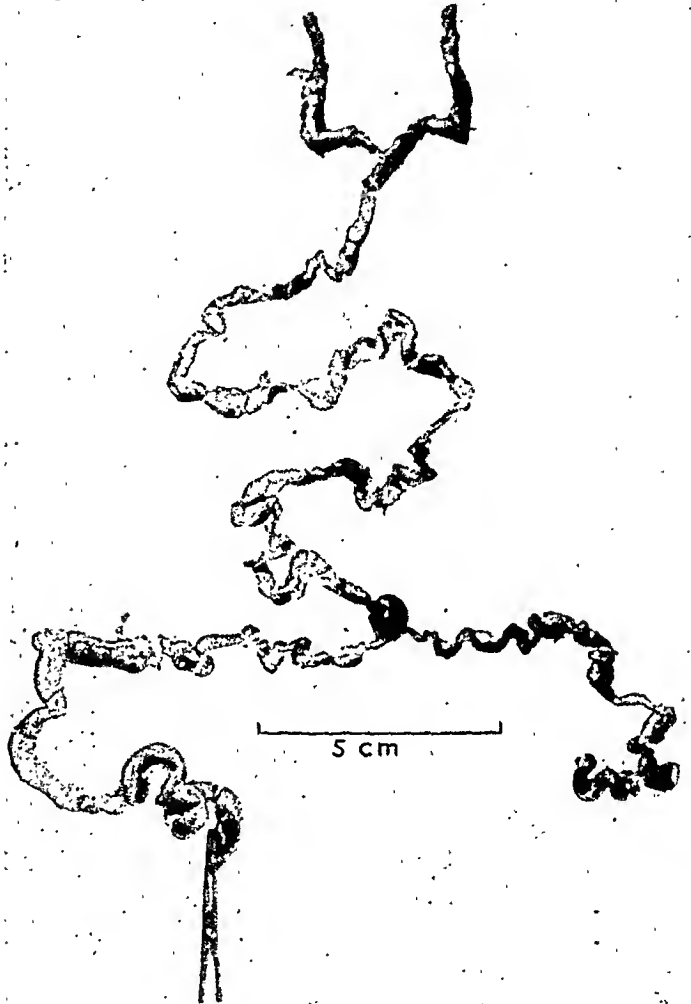


Fig. 5.

Fig. 4.—Common heart with umbilical cord and hepatic veins. (Liver tissue is largely dissected away.)

Fig. 5.—Alimentary tracts showing stomachs, common tract, and large intestine. Note appendices and enlargement at point of separation.

Both twins were dependent on the oxygenated blood received through the umbilical vein which went to the liver on the side of fetus Two. Fetus One had opportunity to receive some of this blood through the capillary connections of the liver, through the foramen ovale, and through any mixing of blood in the large ventricle. The more powerful "left" ventricle evidently forced blood through the interventricular foramen into the "right" ventricle. From here it flowed through the pulmonary arteries to the lungs or into the aorta through the ductus arteriosus.

Gross Observations and Dissection.—For convenience the twins were numbered. The uninjured one was called "One." Superficially it appeared to be a little the larger.

There was a common uncalcified sternum. The two were joined from about the second rib to a point one-half inch below the diaphragm. The cavities and organs were partly common and partly paired. A common diaphragm separated thoracic regions from the common abdomen. The bodies were not exactly opposite but were slightly offset from the midline laterally.



Fig. 3.—Internal organs.

An examination of the umbilical cord showed but three blood vessels, two arteries and a vein. The umbilical cord joined the abdomen at the midline between the two, but both arteries led to fetus Two. The vein led to the common liver.

The large common liver received the umbilical vein on the side of fetus Two. This was traced through the ductus venosus until it joined with the hepatic vein on the same side. A smaller hepatic vein arose from the capillary bed of the liver on the other side and led to the common heart on the side of fetus One. (See Fig. 3.)

Two gall bladders were found. A well-developed one was found between liver lobes on the side of fetus Two and an imperfect one on the other side.

The lungs, esophagus, stomachs, kidneys and spleens were double and appeared normal. The thymus of Two was larger than in One.

Just below the stomachs, there was a fusion of the intestine into one tract. The duodenum of One entered that of Two. Number Two seemed definitely to have the principal tract. The intestine continued as one until an enlargement was formed and the ileum divided. There was more meconium in the large intestine of One than of Two. Anal openings were normal. The appendices of each measured 2.6 cm. (See Fig. 4.)

The heart presented two well-formed atria, a large "left" ventricle on the side of fetus One and a small "right" ventricle on the other side. The foramen ovale was observed.

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Blood could reach the placenta by the umbilical arteries leading from fetus Two but drainage of used blood from One was less direct. This must have depended on mixing the blood in the heart and the passage of blood into the circulatory system of Two from the capillary beds of common tissue.

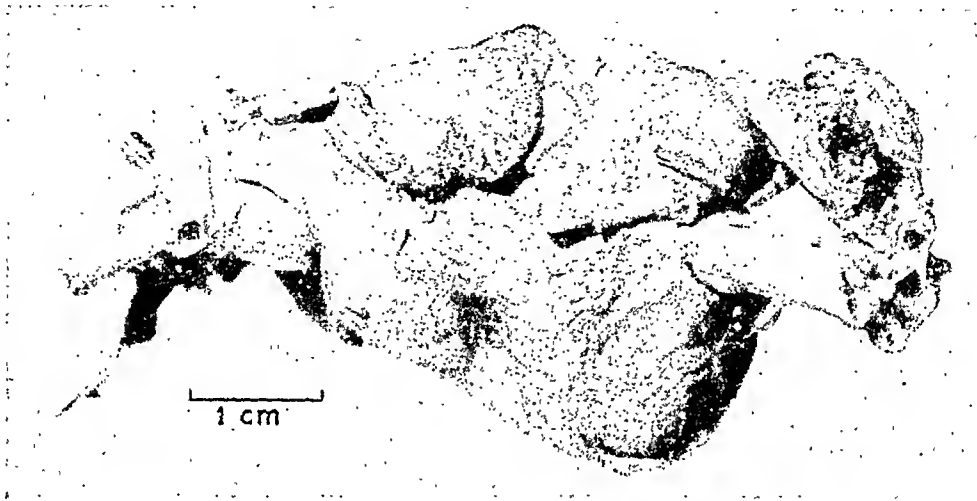


Fig. 6.—Common heart showing aortae, pulmonary artery, and some veins.

Discussion

Two noteworthy hypotheses have been made to explain the development of double monsters. Witschi has cited overripeness of the ovum as a potential cause. Stockard has demonstrated the production of monsters by arresting the development through cooling or through decreasing the oxygen supply.

In our case, the single member of the triplets differed in sex from the conjoined ones. The triplets must, therefore, have developed from two ova. The ova may have developed from the same or different ovaries. According to Arey, the human ovum is believed to be fertile for a period not much longer than one day. And as staleness advances, malformations are more frequent.

There could, however, have been a developmental arrest. The fertilized ovum which developed into the twins may have had an unfavorable descent or uterine implantation, having suffered an arrest through an oxygen deficiency.

Acknowledgments.—The author is indebted to Dr. H. E. Herman of the Corona Hospital for the conjoined fetuses, together with the clinical and delivery history; to Dr. E. Harold Shryock of the College of Medical Evangelists, for advice in examination of the specimen and criticism of the document; and to Dr. L. M. Ashley of the Micro-anatomy Department, for histologic examination; and to Mr. E. N. Hamilton of the Visual Education Department for photographic work.

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Heart and lungs were negative. Blood pressure was 138/90. Fundus 8 centimeters. Pelvic examination revealed a uterus approximately three months' pregnant. Pelvimetry was that of a gynecoid pelvis. Bilateral thoracolumbar incisional scars were noted.

Prenatal Laboratory Data.—X-ray of chest, intravenous urogram, urinalysis, phenol-sulphonphthalein and Fishberg tests all gave normal readings; serology, complete blood count, blood sugar and nonprotein nitrogen were normal.

Prenatal Course.—A tendency toward excessive weight gain between the fourth and fifth months was controlled by restriction of salt, fluids, and diet; there was a 20-pound weight gain during the pregnancy. Urinalysis remained negative until early in the ninth month, when the patient developed a trace of albuminuria. This was accompanied by the appearance of nausea and frontal headaches. Her blood pressure, varying from 132/90 to 118/92, became elevated to 138/100 the last of the seventh month and rose to 140/110 at the beginning of the ninth month. In view of this picture of mild toxemia persisting in the face of adequate prenatal care, the patient was hospitalized for induction of labor.

Hospital Course.—Upon admission Dec. 28, 1946, the patient showed the following findings: blood pressure 136/82; fundus 28 cms.; right occipitoposterior position; head engaged; fetal heart sounds 140; cervix soft, two-thirds effaced, 1 to 2 cms. dilated, membranes intact. Urinalysis showed a trace of albumin.

Labor had not begun following a hot enema and 4 one minute doses of Pitocin, so the membranes were ruptured artificially. An hour later labor began with hard, regular uterine contractions, and at the end of six hours the head had descended in right occipitoposterior position to the low midpelvis, and the cervix had fully dilated. No further progress was evident following an hour and one-half of hard second stage contractions. Under ether anesthesia, following an unsuccessful attempt to rotate the head manually, Tucker-McLane forceps were applied and rotation and extraction of a well-developed, viable, 7 pounds 3 ounces female was performed with no difficulty. The placenta separated via Schultze-Alhfeld, and a midline episiotomy was repaired.

Postpartum Course.—This period was marked by a persistent trace of albuminuria with a few red blood cells and white cells and an elevation of blood pressure developing on the fourth postpartum day, and varying from 178/112 to 140/100 at discharge on rest regime on the tenth postpartum day. A Fishberg test showed a concentration of 1.020 for the second and third specimens combined.

Follow-up Notes.—When seen at four, six, and ten weeks, and again at five and twelve months post partum, the patient had no complaints. Urine examination was normal. The blood pressure on the first two visits was 146/100 and 138/100. Thereafter it varied from 120/80 to 128/96. On check-up a year following delivery, her blood pressure was 108/92; complete blood count was normal; urine was negative; Fishberg 1.028, 1.029, 1.029; phenol-sulphonphthalein was 75 per cent.

As far as treatment of these cases is concerned, judging from personal communications from R. S. Palmer, M.D., of Boston, James L. Poppin, M.D., of Lahey Clinic, J. A. LeFevre, M.D., of the Cleveland Clinic, and from our personal experience, the following should be instituted: (1) Drastic reduction of sodium ion and fat in the diet; (2) moderately high protein intake; (3) minimum weight gain; (4) adequate sedation; (5) sufficient rest; (6) interruption of pregnancy if toxemia appears.

Conclusion

It would seem that some of these hypertensive women may be allowed to attempt pregnancy. It should be remembered, however, that close supervision is necessary because the original hypertension may possibly be aggravated or pre-eclampsia may develop.

We wish to express our appreciation to Drs. Palmer, Poppin, and LeFevre for their communications.

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PREGNANCY FOLLOWING THE SMITHWICK OPERATION FOR HYPERTENSION*

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BECAUSE of the few women who have gone through pregnancy following the Smithwick operation, the addition of one who has delivered one baby prior to this operation and one afterward is instructive.

The Smithwick operation has not only removed certain individuals from that class unfortunately afflicted with hypertension and seemingly increased their longevity, but it would appear to have also given to some young women of this group the opportunity of bearing children with comparative safety.

Kellogg¹ reports ten such cases followed through eleven pregnancies. Blood pressure averaging 190/92 prior to operation, averaged 125/92 afterward and remained within normal limits throughout pregnancy in five cases; in these there was no albuminuria. Four showed moderate hypertension up to 160/90, and two had systolic pressures of 180. The pregnancy of one of the latter had to be interrupted at eight and one-half months. There were nine normal deliveries and two cesarean sections—one a repeat section and one done for a fulminating pre-eclampsia. Ten babies were born alive.

Newell and Smithwick² reported a study of fourteen cases with blood pressures averaging 196/130. Following operation and prior to the pregnancies the blood pressures averaged 135/87; only two had persistent albuminuria. The diagnosis of hypertension was as follows: essential hypertension 7; essential hypertension and associated pyelonephritis 2; two patients developed both during their first pregnancy; there were three cases of malignant hypertension with pyelonephritis in two of these. In nine cases the blood pressure remained within normal limits during pregnancy without albuminuria. In the other five there was little change in blood pressure until the third trimester; in one of these a 4 plus albuminuria necessitated interruption of the pregnancy at eight and one-half months.

Case Report

Mrs. B. presented a case of malignant essential hypertension with one pregnancy prior to and one subsequent to a Smithwick operation. She came to us first July 22, 1946, as a 26-year-old, married, white, gravida ii, who was approximately three months' pregnant. Her past medical history—Scarlet fever during childhood with no known sequelae; Smithwick operation in 1944 at the Crile Clinic for malignant essential hypertension evidenced by tinnitus, dizziness, severe headaches, and blood pressure which varied between 200 to 250 systolic and 150 to 190 diastolic of a year's duration. Following the operation the blood pressure was reduced to 90 to 120 systolic and 70 to 80 diastolic. On a check-up at Cleveland Clinic in February, 1946—"she seemed to be in excellent condition and renal function tests were all quite normal." Menstrual history—Normal twenty-five day cycle of five days' duration. Her last menstrual period was on April 14, 1946. Estimated date of confinement—Jan. 25, 1947. Marital history—Married five years. One previous pregnancy; latter part of 1942; pregnancy marked throughout entire course by severe nausea and vomiting; 8 pounds viable male delivered by family doctor at home by outlet forceps; no other data available. General history—essentially negative. History of present pregnancy—no complaints.

Physical Examination.—Revealed a short, well-developed, slightly obese white female. Her temperature, pulse, and respiration readings were normal. Eye grounds were normal.

*Presented at the regular meeting of the Pittsburgh Obstetrical and Gynecological Society, Jan. 12, 1948.

A REPORT OF EIGHTY CASES OF BENIGN SOLID TUMORS OF THE OVARY WITH SPECIAL REFERENCE TO COMPLICATIONS*

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AMONG the combined total of 24,951 gynecologic admissions at the Elizabeth Steel Magee Hospital and the St. Francis Hospital, there have been 80 cases of benign solid tumors of the ovary. Within the period of time involved, sixteen years at the Magee Hospital and nine years at the St. Francis Hospital, 7,780 specimens of ovarian tissue were submitted for pathologic diagnosis. Hence, the incidence of benign solid tumors of the ovary was 1.03 per cent.

The various types of benign solid tumors of the ovary included:

- A. 73 fibromas
- B. 1 myxofibroma
- C. 1 adenofibroma
- D. 1 neurofibroma
- E. 1 leiomyoma
- F. 3 Brenner tumors

The majority of these tumors were removed secondarily to other pelvic surgery. Complications due to a benign solid tumor of the ovary consisted of gross ascites and torsion with necrosis. The diagnosis of pelvic malignancy was suspected preoperatively in three cases because of ascites, loss in weight, and a large palpable pelvic mass, but these were proved to be benign.

Simple Fibroma of Ovary.—In the 73 cases of fibroma of the ovary, the diameter of the tumor varied from 1 cm. to 20 cm. Of these, 34 cases were associated with uterine fibroids, an incidence of 43.5 per cent. Gross ascites was preoperatively diagnosed in three cases in which the tumor size varied from 5 cm. to 15 cm. Fluid varying from 100 c.c. to 500 c.c. was found at the time of operation in 10 additional patients. The smallest tumor associated with fluid was 1 cm. in diameter.

It was of interest to note that all three patients in whom gross ascites was present showed one of the following pathologic changes in the ovary: large hemorrhagic infarct, gross necrosis, liquefaction necrosis, or degeneration with calcification. Eight other patients showed some form of degeneration and six of these had some ascitic fluid in the abdomen.

A preoperative diagnosis of adenocarcinoma of the ovary was made in one of the three patients with gross ascites. She was a 64-year-old woman admitted with a history of progressive loss in weight, "sudden" ascites, and pain in the abdomen. At operation, a pedunculated fibroma 12 cm. in diameter with partial torsion and necrosis was found. Approximately 3,000 c.c. of blood-tinged fluid was removed from the abdomen. The second patient was a 46-year-old woman admitted with a preoperative diagnosis of granulosa-cell tumor and uterine fibroids. A fibroma of the ovary, 8 cm. in diameter, associated with large pedunculated fibroids was found. There were approximately 1,500 to 2,000 c.c. of plasma-like fluid removed from the abdomen. The third patient was admitted with a preoperative diagnosis of ovarian cyst and uterine fibroids. She was 46 years old and her complaint was irregular,

*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Oct. 6, 1947.

CONSERVATIVE TREATMENT OF PLACENTA ACCRETA WITH SUBSEQUENT NORMAL PREGNANCY

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(From the O'Connor Hospital)

IT IS generally accepted, and most textbooks recommend, that a retained placenta be removed surgically or manually. It is also generally believed that a placenta accreta or increta must be treated by hysterectomy.

Greenhill, in the ninth edition of DeLee-Greenhill, states that, in spite of fourteen reported cases where the placenta was allowed to remain and all the women survived, he believes that abdominal hysterectomy is the treatment of choice.

The following is a case report of placenta accreta or increta that was treated conservatively with no harmful effects. One year subsequently the patient had a normal delivery with a normal third stage.

D. M., aged 31 years, who had been under treatment for infertility, was examined on June 11, 1946. Her last normal menses was April 5, 1946, but she reported having had a scant one-day period on May 10, and another on June 1. Examination at this time revealed a slightly enlarged, soft uterus with a known previously existing cystic tumor in the right adnexa. A presumptive diagnosis of pregnancy was made.

She was not seen again until August 16, 1946, because she had not kept her scheduled appointment, nor made a new one. She came in at this time because of lower abdominal cramps and slight bleeding, both of a week's duration. Examination revealed a uterus the approximate size of a four months' pregnancy. The cervix was effaced, dilated 2 cm., and the amniotic sac was visible. She was sent directly to the hospital and treated with absolute bed rest, sedation, and progesterone. Twenty-four hours later, she was delivered of a 22 cm. fetus that showed no gross abnormalities. All efforts to express the placenta failed. Since there was very little bleeding, she was returned to bed and put on an Ergotrate regime. The next morning she was taken to the operating room where, under deep anesthesia, an attempt was made to remove the placenta manually. Palpation of the uterine cavity by both the operator and his assistant revealed no line of cleavage of the placenta. It was impossible to determine where the placenta ended and the uterine wall began. Because there was practically no bleeding, it was decided to follow a conservative course, and the patient again was returned to bed. She was kept in the hospital one week under treatment with Ergotrate, penicillin, and sulfadiazine. No serious bleeding nor evidence of infection developed so she was transferred home. She remained in bed at home for three weeks, during which time the uterus drained a bloody purulent lochia. Her only complaint was of cramps and pains in the legs, especially at night. Two weeks after the delivery, the fundus was not palpable abdominally. From the fourth to eighth week post partum the uterine drainage was of a bright bloody character and very moderate in amount. All discharge stopped on October 10, 1946. On the 19th of October the uterus was found to be of normal size, anterior, firm, and mobile. The right adnexal mass was still present.

She had a one-day menses on November 7, and a scant three-day period on December 15. On February 1, 1947, a presumptive diagnosis of six weeks' pregnancy was made and treatment for habitual abortion instituted. Her pregnancy was essentially normal throughout and she was delivered of a normal 7-pound infant on September 24, 1947, after an eleven-hour labor. A grossly normal placenta was delivered two minutes later by simple expression. Postpartum bleeding and the entire puerperium were normal.

It may be concluded from this case that placenta accreta, in the absence of unusual bleeding, can be treated conservatively without risk and that subsequent pregnancy may be entirely normal.

While collecting material for this report, gross ascites was also noted in two patients with large degenerating theca-cell tumors. Fluid varying from 100 c.c. to 500 c.c., not detected preoperatively, was found in ten patients with a benign solid tumor of the ovary and six of these patients had degenerative changes within the tumor mass. All the cases with gross ascites had also degenerative changes present.

The benign solid tumors of the ovary were asymptomatic with the exception of those cases in whom complications occurred such as ascites, degeneration causing pain, or torsion of the adnexa.

All three Brenner tumors were removed because of a painful, enlarged mass in the adnexa with considerable associated tenderness on pelvic examination. The patients varied between the ages of 21 and 44 years.

The patients with simple fibromas, or one of the rarer forms of fibromas, varied between the ages of 19 and 67 years, but all tumor complications occurred in patients from 41 years to 67 years.

Meigs' syndrome (fibroma of ovary, ascites, and hydrothorax) was not present in any of the cases with gross or minimal ascites.

Granulosa cell tumors were not included in this report.

Summary

1. A report of 80 cases of benign solid tumors of the ovary is presented.
2. The incidence of benign solid tumors of the ovary is approximately 1 in 97 specimens of ovarian tissue.
3. The incidence of the various tumors based on the number of specimens of ovarian tissue submitted to the laboratory are:

| | |
|-------------------------|---------------------------------------|
| 1. Fibroma | 1 in 106+ specimens of ovarian tissue |
| 2. Leiomyoma of ovary | 1 in 7,780 |
| 3. Myxofibroma of ovary | 1 in 7,780 |
| 4. Adenofibroma | 1 in 7,780 |
| 5. Neurofibroma | 1 in 7,780 |
| 6. Brenner tumors | 1 in 2,593+ specimens. |

4. Ascites (gross or minimal) was the most common complication.
5. The presence of abdominal ascites with a pelvic tumor mass does not always mean malignancy.
6. The tumor mass causing the ascites may be a benign solid tumor of the ovary or a large degenerated uterine fibroid.

Note.—Appreciation is extended to Dr. B. Z. Cashman for his guidance in the preparation of this paper.

profuse vaginal bleeding. At operation, a fibroma 5 cm. in diameter associated with small uterine fibroids was removed. There were approximately 2,000 c.c. of straw-colored fluid present.

Myxofibroma of Ovary.—A 47-year-old patient was admitted with a preoperative diagnosis of large uterine fibroids. She had complained of left-sided pain for 10 years and gradual enlargement of the abdomen for 3 years; ascites was detected preoperatively. At operation, a tumor of the ovary was removed measuring 12 cm. by 15 cm. by 11 cm. There was considerable necrosis present. Approximately 2,000 c.c. of straw-colored fluid was removed from the abdomen at the time of operation.

Adenofibroma.—There was one case of an adenofibroma associated with endometriosis of the ovary. The history was that associated with pelvic endometriosis and on pelvic examination an enlarged, painful ovary was palpable. At operation it was noted that the ovary was not adherent and measured 7 cm. by 5 cm. by 4 cm. The remaining pelvic viscera appeared grossly normal and there was no ascites noted.

Neurofibroma.—A neurofibroma 4 cm. in diameter was removed secondarily to an acute ulcerative appendicitis in one case. The ovary was removed only because of its accessibility and also the possibility that it might have caused the patient trouble at a later date.

Leiomyoma of Ovary.—A diagnosis of leiomyoma of the ovary with liquefaction necrosis and cyst formation associated with gross ascites was made in one patient in whom a probable ovarian malignancy was considered preoperatively because of lower abdominal pain, gradual enlargement of the abdomen, detectable ascites, and loss of weight. The diagnosis of a benign solid tumor of the ovary was established histologically.

Fibromas Associated with Abdominal Malignancy.—In one patient, aged 67 years, a preoperative diagnosis of cystic ovaries and probable ovarian malignancy was made. At operation, a carcinoma of the right ovary measuring 5 cm. by 8 cm. by 8 cm. and a fibroma with degeneration measuring 4 cm. by 6 cm. by 4 cm. was found in the left ovary.

The second patient, aged 44 years, was admitted with a preoperative diagnosis of uterine fibroids. Her chief complaint was "mass in the abdomen" and "weight in the abdomen." At operation, a fibroma of the ovary with necrosis, measuring 16 cm. by 10 cm. by 10 cm. was removed. There was also an adenocarcinoma of the cecum necessitating resection of the colon and a transverse ileocolostomy.

Torsion of an Adnexa Associated With a Benign Solid Tumor of the Ovary.—The tumors varied from 2 cm. to 7 cm. in diameter and this complication occurred in five patients. Gross ascites was found in one patient.

Brenner Tumors.—The three Brenner tumors included in this report were associated with uterine fibroids. The tumor size varied from 2 cm. to 6 cm. in diameter. Lower quadrant pain and tenderness on pelvic examination was found in all three cases. There was no associated ascites. A small fibroma in the contralateral ovary was found in one patient.

Discussion

The most outstanding complication associated with a benign solid tumor of the ovary in this series of cases was gross ascites. This occurred in five cases. The association of a large tumor mass in the pelvis with ascites accompanied with loss in weight accounted for the preoperative diagnosis of pelvic malignancy in three patients. Ascites associated with an abdominal tumor is most often associated with a malignancy, especially carcinoma of the ovary. One need only refer to the vastly accumulated literature to remind himself that this is not always true. This is well exemplified by a case not included in this report in which a preoperative diagnosis of malignant granulosa-cell tumor and uterine fibroids associated with gross ascites was made in a 41-year-old patient. At the time of operation, approximately 2,000 c.c. of ascitic fluid was removed. A large benign, posteriorly located fibroid was found which extended to the umbilicus and which had undergone considerable cystic degeneration.

extraction, 5 cases; extraperitoneal section, 1 case; and spontaneous, 18 cases. All midforceps were in primigravidas and all the spontaneous deliveries occurred in multigravidas.

Duration of Action and Effect Upon Labor.—The intravenous administration of 8 to 10 grains of vinbarbital sodium produces sleep within several minutes. This sleep is restless to varying degrees in half of patients. Bedside nurses are a necessity. Fifteen of the patients in this series (10 per cent) were so extremely restless and uncontrollable that constant nursing attention and restraint were necessary. Three of these patients fell out of bed when not watched.* Administration of additional vinbarbital sodium, unless carried to the point of anesthesia, is not the solution to the problem of the extremely restless patient. The answer is attention and restraint. In 135 cases, delivery occurred from thirty minutes to seven hours after the initial administration of the drug. The duration of good analgesia-amnesia was four to six hours. In ten cases, because of waning effect and increasing restlessness, the additional intravenous injection of half the initial dose was needed to carry the patient through to delivery. In four cases, the administration of vinbarbital sodium was discontinued after one or two additional doses because of prolonged labor with slow progress in spite of seemingly adequate uterine contractions. The prolonged labor was in no way attributable to the medication. In one case, after the initial dose of 10 grains of drug with the patient in good labor, uterine contractions were practically arrested and fourteen hours later, with the uterus still refractory and the cervix incompletely dilated, an extraperitoneal section was done. The last five unsuccessful cases were in primigravidas with posterior positions. This type of failure was not limited to the author's cases. Consequently, after experience in these cases, vinbarbital sodium was not used in posterior positions entering into labor slowly, with contractions of only fair quality and with the cervix firm and poorly effaced.

Degree of Analgesia-Amnesia.—Complete relief of pain and complete amnesia were experienced by 122 patients. Faint or partial recall of events and pain were reported by twenty patients. This experience of pain and the recall of events were associated with that period four to six hours after the initial injection, when another injection was necessary or when delivery was so imminent that there was little point to additional medication. Orientation and poor relief of pain were encountered in three patients. Not included are the five patients who had the drug discontinued, although all had good results for the period of usage.

Period of Recovery Following Delivery.—Following delivery (under cyclopropane) patients would sleep deeply for four to twelve hours. This would, on occasion, cause alarm to the patient's relatives. While gradually waking to full consciousness, patients were frequently restless and would get out of bed unless watched. Upon waking, patients, for the most part, experienced drowsiness, vertigo, blurring of vision, and poor recall—of slight to marked degree—until twelve to thirty-six hours after delivery. This "hang-over" was only slightly objectionable to most, but three patients were adamant that they never be given the drug again.

Resuscitation of Infants.—In 149 viable infants, 119 breathed spontaneously. The time interval for clamping the cord, aspirating mucus and fluid from nose and mouth, and clearing the pharynx with a suction catheter was 3 minutes. Flagellation of the feet and buttocks and massage of the base of the spine were employed. If, after this interval, no voluntary respiratory movements were evident and if the infant was limp and deeply cyanotic, artificial resuscitation with

*A number of patients outside of this series, to whom scopolamine was not given showed little change in regard to restlessness.

INTRAVENOUS VINBARBITAL SODIUM FOR OBSTETRIC ANALGESIA*

MATHIAS F. F. KOHL, M.D., PH.D., ROCKFORD, ILL.

(From The City Hospital of Akron)

THE use of intravenous vinbarbital sodium for the rapid relief of pain during the conduct of labor has been favorably reported.^{1, 2} In approximately 150 cases, Lewis² gave an average intravenous dose of 15 grains vinbarbital sodium (range 5 to 25 grains) as the sole analgesic-anesthetic agent for the conduct of labor and delivery. About 60 per cent of his cases were delivered within thirty minutes of the initial injection and all cases were delivered within two hours. There was no interference with the progress of labor. Spontaneous delivery occurred in 33 per cent of primigravidas and 60 per cent of multigravidas. Respirations were spontaneous in 83 per cent of infants, while mild asphyxia, requiring no resuscitation, was present in another 13 per cent.

Intravenous vinbarbital sodium for combined analgesia-anesthesia was used by Lewis primarily in patients not seen or not requiring medication until delivery was imminent. It was the purpose of this study to extend the use of intravenous vinbarbital sodium to the earlier painful phases of the first stage of labor, as soon as uterine contractions are strong and productive of cervical dilatation. The requirements made upon an intravenous agent for relief of pain with a minimum of undesirable effects are more exacting under such a condition than when given at the last hour in large amounts to produce narcosis.

This study is an evaluation of 150 deliveries (68 primigravidas and 82 multigravidas) in which vinbarbital sodium was used intravenously in conjunction with intramuscular scopolamine hydrobromide. These are not consecutive cases, since experience, as will be shown, necessitated discontinuance in selected cases. The author has also been benefited by the experience of other members of the Obstetrical Service of The City Hospital of Akron who have similarly used vinbarbital sodium in well over 500 cases.

Criteria for Administration and Dosage Used.—An initial intravenous injection of 8 or 10 grains of vinbarbital sodium, depending on the size and weight of the patient, was given to primigravidas with strong four- to five-minute uterine contractions and cervical dilatation of 3 to 4 cm., and to multigravidas complaining with severe three-minute pains or with pains of lesser degree if cervical dilatation was 4 cm. The drug was given carefully over a two-minute period. Extravasation into the tissue caused painful tissue induration. Simultaneously, scopolamine hydrobromide $\frac{1}{150}$ grain (with 10 grains vinbarbital sodium) or $\frac{1}{200}$ grain (with 8 grains vinbarbital sodium) was given intramuscularly. If additional amounts of vinbarbital sodium were needed, it was repeated in half the initial dose, i.e., 4 or 5 grains. Delivery was conducted under cyclopropane anesthesia, for the most part, or ether anesthesia.

Types of Delivery.—In 150 cases (68 primigravidas, 82 multigravidas) delivery was effected as follows: low forceps, 120 cases; midforceps, 6 cases; breech

*Vinbarbital sodium is the nonproprietary name for sodium 5-ethyl 5-(1-methyl-1-butenvl) barbiturate and is distributed under the name of Delvinal Sodium. The material used in this study is a solution containing 1 grain per c.c. and was provided by the Medical Research Division of Sharp and Dohme, Inc.

was given for the control of pain during labor. The medication is most successful in cases delivering within four to six hours. Constant nursing attention is necessary because of restlessness. Complete analgesia-amnesia occurred in 85 per cent of patients. Artificial resuscitation was necessary in 20 per cent of infants for either primary respiratory delay or secondary respiratory depression. There was a high incidence of apnea and cyanosis in infants during the first day of life. Properly used and with constant attention to limitations, intravenous vinbarbital sodium is a valuable drug in the obstetrician's armamentarium for the relief of pain.

References

1. Evans, J. R.: AM. J. OBST. & GYNEC. 47: 821, 1944.
2. Lewis, M. S.: AM. J. OBST. & GYNEC. 51: 395, 1946.

an alternating positive-negative pressure machine was started. Experience dictated that procrastination was not in order. Primary mechanical resuscitation was necessary in the case of twenty-one infants, with the time required usually being two to five minutes. In nine infants responding normally and breathing regularly, a secondary respiratory depression occurred at intervals varying from five to thirty minutes after birth. Resuscitation in these cases took usually one to ten minutes depending upon how soon the depression was noticed. It was imperative to watch all infants closely, even though they were breathing normally, for the possible secondary respiratory failure. There were five infants requiring longer than ten minutes' resuscitation for the establishment of regular breathing, namely, 12, 15, 20, 23, 180 minutes. This last instance was an infant breathing normally after three minutes of resuscitation for respiratory delay at birth. Thirty minutes after birth, the infant was found in its crib for all practical purposes dead. Only heroic efforts by a well-trained anesthetist over a three-hour period salvaged this life.

*Effect on the Newborn.**—This is an important, although much neglected, aspect of any study having to do with obstetrical analgesia-anesthesia. Twenty-five infants were chosen at random from cases reported here and other cases of colleagues. In 12 cases, respiration had been spontaneous; in 9 cases, primary respiratory depression necessitated one to ten minutes' resuscitation; and in 4 cases, a secondary respiratory failure required four to ten minutes' resuscitation. In this group of 25 infants, 9 infants required stimulation and oxygen because of periods of apnea and cyanosis during the first twenty-four hours of life. This was not carried into the second day of life. The "vinbarbital" babies were inclined to be drowsy and sluggish, difficult to keep awake for feeding, limp, cold, and full of mucus. Of the 25 babies, 16 were so depressed the first day; 9, the second day; 3, the third day; 1, the fourth day. Breast feeding was very unsatisfactory. These babies all required extra nursing attention.

Fetal and Maternal Complications.—The three fetal deaths in this series (anencephalic monster, hydrocephalic monster with spina bifida, normal stillborn with prolapsed cord) were not attributable to the method of analgesia. There were three infants in this series, premature by gestation and weight, that breathed spontaneously and did well. There was one case of erythroblastosis fetalis (not on the basis of Rh). Maternal complications were the usual for any series of 150 cases. The three patients falling out of bed and the patients requiring section for arrested labor can be considered to have had complications attributable to vinbarbital sodium.

Indications for the Use of Vinbarbital Sodium.—From experience in these 150 cases and information gained from approximately 500 cases of colleagues, it is considered advisable to reserve the use of intravenous vinbarbital sodium as outlined in this study to multigravidas and those primigravidas in whom labor promises to be rapid, in so far as can be judged from the quality of uterine contraction, station of the presenting part, and condition of the cervix. Cases of pelvic contraction and malposition are necessarily excluded. Vinbarbital sodium is contraindicated in the presence of uterine inertia or cervical rigidity, despite the impression gained in many cases that relaxation of the tense, apprehensive patient by the drug facilitates cervical dilatation by the contracting uterus and that labor is seemingly accelerated.

Summary and Conclusions

One hundred and fifty deliveries are reported in which intravenous vinbarbital sodium, supplemented by intramuscular scopolamine hydrobromide,

*I am indebted to Dr. Ralph Wymer, Resident in Obstetrics and Gynecology, for this preliminary data.

drome, I can only say that, in my published report, I have quoted from a letter which Dr. Meigs wrote me and which I have on file. I agree to a great extent with Dr. Millett's remarks about the postoperative chest taps. Nevertheless, it is true that his case and McFec's were the only ones that reported a postoperative thoracentesis and theirs were the only cases of cystadenomas. Finally, while it is obviously important that it be understood that benign cystic tumors can produce ascites and hydrothorax, nevertheless, when benign (though potentially malignant) cystic tumors are included in the category of Meigs' syndrome, there is a grave danger that the concept of its benignity will be lost. I believe, therefore, that by limiting cases of Meigs' syndrome to solid tumors, we thus preserve in the medical mind the indisputable lack of malignancy of the syndrome even though occasional cases of benign cystic tumors which produce ascites and hydrothorax must be excluded.

HERBERT J. SIMON, M.D.

P.S. Since writing the above, I have read Samuel S. Rosenfeld's case report, "A Pseudomucinous Cyst of the Ovary With Ascites and Hydrothorax" in the *New York State Journal of Medicine*, of March 1, 1948. Dr. Rosenfeld told me that he did not have to do a postoperative chest tap on his patient. I call attention to this in spite of the fact that it weakens my position and strengthens Dr. Millett's.

H. J. S.

20 EAST 76TH STREET
NEW YORK.
APRIL 30, 1948

Correspondence

The Meigs' Syndrome

To the Editor:

I have read with great interest the excellent report on the case of Meigs' Syndrome in the JOURNAL 53: 1042, 1947, by Dr. Herbert J. Simon. He has illustrated beautifully the most important point in these types of cases; namely, that even though the patient's clinical condition appears to be very grave, removal of the offending tumor gives complete and lasting relief.

In reference to the case report of Millett and Shell which appeared in the *Am. J. M. Sc.* 209: 327 (March), 1945, Dr. Simon takes us to task, stating that a multilocular pseudomucinous cystadenoma of the ovary should not be reported as a case of Meigs' syndrome and quotes Dr. Meigs as follows:

"I don't think that papillary tumors or any kind of tumor that is not of the solid variety should be considered as cases of Meigs' syndrome."

I am unable to square this statement with the following statement by Dr. Meigs to us prior to the publication of our case report; this statement appears as a footnote in our article and is as follows:

"Believing that, in general, eponymic names of diseases should be restricted closely to the conditions as described by the original author, we asked Dr. Meigs if he thought that the term was justified in this case, which is not a fibroma, as originally described by him. We may say that he thinks that it is justified, and that the various types of primary lesions should be considered, from this point of view in one group."

The question of the postoperative chest tap is, I believe, of no great importance at this time. The syndrome has been fixed as a clinical entity and, inasmuch as the fluid did not recur with the removal of the offending tumor after four years when the patient was last seen, I believe we can definitely state that cause and effect have been clearly established.

I do wish that more of these case reports could be published more often in those journals relating to internal medicine and cardiology, to familiarize the men in these fields with this syndrome, as they are usually the first to see these types of cases. It is curious that nowhere in any textbook relating to the above specialties does Meigs' syndrome appear as a point of differential diagnosis. Perhaps the obstetricians and gynecologists can be persuaded to send their reports to journals relating to medicine and cardiology so as to familiarize the men in these fields with the syndrome, so that the surgeons can be called in much earlier to obtain the dramatic reversal in the clinical status of the patient.

JOSEPH MILLETT, M.D.

501 FULTON AVENUE
HEMPSTEAD, N. Y.
MARCH 3, 1948

Reply by Dr. Simon

To the Editor:

I am grateful for the opportunity of answering Dr. Millett's letter.

First, I wish to thank Dr. Millett sincerely for his flattering remarks about my report. Second, I heartily concur with his suggestion that more of these cases be reported in journals of internal medicine and cardiology in order to familiarize our internist brothers with the existence of the entity. (Dr. Millett saw the wisdom of this before he published his report and accordingly it appears in the *American Journal of Medical Sciences*.)

In reply to the question brought up in Dr. Millett's letter as to Dr. Meigs' personal opinion of the desirability of cystic tumors being included in the category of Meigs' syn-

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Ludwig Emge. *Secretary*, Norman Miller, Ann Arbor, Mich. Next meeting, May, 1949, Hot Springs, Va.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, James R. Bloss, Huntington, W. Va. *Secretary*, Leroy A. Calkins, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 7-9, 1949.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, S. R. Norris, Jacksonville, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Williamsburg, Va., February 10 to 12, 1949, at the Williamsburg Inn and Lodge.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
- New York Obstetrical Society.** (1863) *President*, Albert H. Aldridge. *Secretary*, Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Carl Bachman. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Herbert E. Schmitz. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Alexander E. Dunbar. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Stanley T. Garber. *Secretary*, Joseph G. Crotty, 146 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, James Hodgkiss. *Secretary*, Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.
- Obstetrical Society of Boston.** (1861) *President*, Paul Gustafson. *Secretary*, H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Henry N. Shaw. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.
- Washington Gynecological Society.** (1933) *President*, William J. Cusack. *Secretary*, John Parks, 901 23 St., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Woodard D. Beacham. *Secretary*, Harry Meyer, 3439 Prytania St., New Orleans, La. Meetings held October, November, January, March, and May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

Items

American Board of Obstetrics and Gynecology

The next scheduled examination (Part I) written examination and review of case histories, for all candidates, will be held in various cities of the United States and Canada on Friday, February 4, 1949. New Applications may be made until November 1, 1948. Application forms and Bulletins are sent upon request made to

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.,
1015 Highland Building,
Pittsburgh 6, Pennsylvania.

Prize Award

The South Atlantic Association of Obstetricians and Gynecologists announces the establishment of "The Foundation Prize." Authors of papers on obstetrical or gynecological subjects desiring to compete for the prize may obtain information from Dr. E. D. Colvin, Secretary-Treasurer, 1259 Clifton Road, N. E., Atlanta, Ga.

Erratum

In the article by Joseph A. Kurcz and Mahlon S. Sharp, entitled "Congenital Absence of One Ovary Associated With Contralateral Tubal Pregnancy," in the June issue of the JOURNAL, on page 1065, the Woman's Hospital, from which the article was written, should have been followed by the address, Detroit, Michigan.

Dr. Sharp's present address is 512 Olds Tower Building, Lansing, Mich.

- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Le Roy H. Sadler. *Secretary-Treasurer*, John W. Records, 301 Northwest 12 Street, Oklahoma City.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Herschel Murphy. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, Frank C. Spencer. *Secretary-Treasurer*, H. McLeod Patterson, 202 King Kalakaua Bldg., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists.** *President*, Duncan R. Neilson. *Secretary-Treasurer*, David M. Baker, 520 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, P. K. Champion. *Secretary*, L. J. Lohr, 2676 Salem Ave., Dayton, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.
- Queens Gynecological Society.** (1948) *President*, Moses Cohen. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held third Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.
- Mississippi Association of Obstetricians and Gynecologists.** (1947) *President*, Walter Simmons. *Secretary*, Richard H. Street, Jr., The Street Clinic, Vicksburg, Miss. Meetings held semiannually.
- Florida Obstetrical and Gynecological Society.** *President*, Charles J. Collins. *Secretary*, Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.

- St. Louis Gynecological Society.** (1924) *President*, Joseph A. Hardy, Jr. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Warren E. Massey. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, O. W. Picard. *Secretary*, Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Raymond J. Pieri. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Donald J. Thorp. *Secretary-Treasurer*, Charles D. Kimball, 734 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.
- Denver Gynecological and Obstetrical Society.** (1942) *Secretary*, Warren W. Tucker, 1820 Gilpin St., Denver 6, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Henry A. Sincok. *Secretary-Treasurer*, Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, R. C. Hall. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo; N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, John Boyd. *Secretary-Treasurer*, William Durwood Suggs, Monument Ave. and Lombardy St., Richmond, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Dana Cox. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Robert S. Millen. *Secretary-Treasurer*, Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, H. J. Lesnick. *Secretary*, Mark Daniel, 2344 Davidson Ave., Bronx 53, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, H. H. Skinner, Yakima, Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Joseph G. Webster. *Secretary*, William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday; May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, Carl E. Krugmeier. *Secretary-Treasurer*, A. M. McCausland, 3780 Wilshire Blvd., Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, S. B. Conger. *Secretary-Treasurer*, Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.
- Minnesota Society of Obstetrics and Gynecology.** *President*, Everett C. Hartley. *Secretary*, John Haugen, 100 E. Franklin Ave., Minneapolis, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, M. C. Wilson. *Secretary*, George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Charles F. Moon. *Secretary*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

the individual reports of much smaller series would have been, particularly since they represent a cross section of climatic conditions, dietary variations, geographic distribution, and general obstetric care throughout the United States.

Basis for the Use of Diethylstilbestrol in Pregnancy

The observation that a marked rise in estrogen excretion at about the tenth to twelfth week of normal pregnancy was followed by an equally marked drop in chorionic gonadotropin (C.G.) was reported by Smith and Smith in 1936.¹ In 1938 the same phenomenon was observed following estrogen administration to pregnant women.² Their quantitative studies of estrogens, pregnanediol, and serum C.G. in pregnancy suggested to them that an abnormal rise in serum C.G. might reflect failing utilization of this factor for the production of the placental steroids.^{2, 3} Since studies in both pregnant and nonpregnant women had indicated that a rise in estrogen always preceded any increased secretion of progesterone, it was logical to propose that estrogens were in some way causally related to corpus luteum activity in the nonpregnant women and to the utilization of C.G. in pregnancy for the placental production of progesterone. The results of experiments by Heekel and Allen in 1939⁴ lent support to this idea by demonstrating that progesterone secretion could be maintained and delivery postponed in the pregnant rabbit by estrogen administration. In 1941 Smith and Smith⁵ summarized their findings on estrogen and progesterone metabolism in women, and concluded from the results that estrogen oxidation products rather than estrogens per se were responsible for the progesterone stimulating effect of estrogen, through pituitary stimulation in nonpregnant women⁶ and through causing increased utilization of C.G. in pregnancy.⁵ It was demonstrated experimentally that progesterone, which depresses the rate of estrogen oxidation, also markedly inhibited the pituitary stimulating properties of estrone.⁷ In any attempt to enhance progesterone secretion with estrogens in human pregnancy, therefore, more estrogen would have to be given than could be metabolized by the available progesterone.⁸ It was found, however, that diethylstilbestrol, unlike the naturally occurring estrogens, was not depressed in its pituitary stimulating effects by the presence of progesterone⁹ and might theoretically, therefore, provide an ideal agent for preventing progesterone deficiency in pregnancy. Experimental support of the concept that stilbestrol would enhance the utilization of C.G. for the production of progesterone had been supplied by the finding that this estrogenic compound augmented the ovarian response of hypophysectomized rats to C.G. resulting in corpus luteum formation, an effect which cannot be achieved in the hypophysectomized animal either by C.G. or stilbestrol alone.¹⁰

More direct support of the concept was supplied by the results of quantitative assays for urinary pregnanediol and serum C.G. in two diabetic women with bad obstetric histories to whom stilbestrol was being administered as a preventive measure against late pregnancy accidents.^{11, 12} A rise in urinary pregnanediol and a drop in serum C.G. was noted upon the initiation of stilbestrol therapy, whereas a reversal of this effect occurred each time that the drug was experimentally discontinued. This observation has been repeatedly confirmed in a series of patients with bad obstetric histories who are now being followed at the Boston Lying-in Hospital. So far as our present knowledge takes us, therefore, the concept seems tenable that stilbestrol causes an increased secretion of progesterone in human pregnancy (probably by the placental syncytium) through causing an increased

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VOL. 56

NOVEMBER, 1948

No. 5

Original Communications

DIETHYLSTILBESTROL IN THE PREVENTION AND TREATMENT OF COMPLICATIONS OF PREGNANCY*

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(From the Fearing Research Laboratory, Free Hospital for Women)

THE present study, a clinical evaluation of our concept concerning the action of diethylstilbestrol in human pregnancy, was started in the fall of 1943 and is still in progress.‡ To date complete reports upon 632 pregnancies have been received and analyzed at the Fearing Research Laboratory. Both ward and private patients are represented, although the majority were private. The writer would like to emphasize that the credit for the present contribution belongs to the 117 obstetricians who not only followed our recommendations but were willing to pool their results and to send to us a complete record of each treated case.§ Some had sufficient material for a personal communication (D. Abramson, Boston, Mass.; L. Woods and W. Calden, Oakland, Cal.; P. Gustafson, Boston, Mass.; G. Heels, Cambridge, Mass.; C. L. Sullivan and R. J. Heffernan, Boston, Mass.; and H. B. Nelson, Boston, Mass.). The pooled results are, of course, very much more significant than

*Presented before the Norfolk District Medical Society, Boston, Mass., Feb. 24, 1948.

†With the collaboration of 117 obstetricians from 48 cities and towns in New York, New Jersey, Pennsylvania, District of Columbia, Illinois, North Carolina, Virginia, Texas, New Mexico, California, and all of the New England States.

‡E. R. Squibb & Sons has supplied 25 mg. tablets of stilbestrol for most of the cases treated.

§In order to be certain of procuring a record on every treated patient, each doctor, upon receiving an allotment of stilbestrol, was required to send in a card for each patient to be treated, stating the name of the patient, the last menstrual period, and the indication for therapy. These cards were filed under the doctor's name according to the expected date of confinement. Final record sheets were also supplied and, if not returned soon after a patient was due to deliver, follow-up letters were sent to the obstetrician. In this way we hoped to be sure of receiving records on all treated patients and to overcome the tendency of any busy practitioner to forget short periods of therapy that terminated in failure. We believe we have been fairly successful in this, since our only incomplete records to date are on patients who moved away in the middle of a pregnancy and could not be traced by their obstetricians. There is the possibility, however, that cards were not sent in on all cases. In tabulating the data, however, we have analyzed all past pregnancies of these patients, and used this means of evaluating results. It would seem that the significance of any differences noted between treated pregnancies and the untreated complications of the same group of patients would not be materially diminished by lost cases.

dosage is increased by 5 mg. at two-week intervals to the fifteenth week when 25 mg. daily are being taken. Thereafter, the daily dosage is increased by 5 mg. at weekly intervals. Administration is discontinued at the end of the thirty-fifth week since a drop in estrogen and progesterone normally precedes the onset of labor. For the prevention of late pregnancy accidents stilbestrol is started as early as possible, but no later than the sixteenth to nineteenth week, since a deficiency of estrogen oxidation products has been demonstrated during the second trimester in these patients.⁶ The initial dosage is always the one for the particular week of pregnancy when therapy is begun.

Clinical Results

The case reports have been divided according to the indications for stilbestrol therapy.

Stilbestrol for threatened abortion.—(Table I.) In this group are included only patients who were bleeding, with or without cramps, between the sixth and twenty-first weeks of pregnancy. Although the amount of bleeding was not specified in many of the cases, it was described as definite bleeding as opposed to staining. Bleeding at about the time of the first missed period was not considered threatened abortion, since endometrial bleeding at the site of implantation has been shown to occur normally and might well be sufficient to result in outside bleeding at this time.¹⁵ Thirty-four patients whose only symptom was cramps are also omitted from this group (32 of these, or 94 per cent, carried) but many of them had had previous abortions, and are therefore included in Table II.

TABLE I. STILBESTROL FOR ABORTION; DEFINITELY FOR THREATENED ABORTION (BLEEDING 7 OR 8 CRAMPS WKS. 6-21); 219 CASES*

| PREVIOUS ABORTIONS | NO. OF CASES | CARRIED TO 28 WEEKS (PER CENT) | LIVING AND WELL BABIES (PER CENT) |
|--------------------|--------------|-----------------------------------|---|
| 0 | 143 | 74 | 70 |
| 1 | 46 | 88 | 77 |
| 2 | 17 | 82 | 72 |
| 3 or more | 13 | 83 | 82 |
| Total | 219 | 78 | 72 |

*Including 9 cases on too low dosage, 6 of whom aborted and 15 cases on too high dosage, 4 of whom aborted.

Seventy-eight per cent of the 219 women carried to twenty-eight weeks, and 72 per cent obtained living children. Hertig and Livingstone,¹⁶ in reviewing the literature on this subject, concluded that approximately 40 per cent of threatened abortions do not abort regardless of treatment. The highest spontaneous cure rate that they quote from the literature is 50 per cent. Since the cases reported in Table I received no supplementary therapy other than bed rest and sedation, the increased salvage must have been due to stilbestrol and is highly significant.* Twenty-two of the abortuses were examined pathologically and 17, or 77 per cent, were found to be defective. There were no abnormalities in the fetuses that were carried.† It is note-

*Throughout this communication the difference between our observed incidence of any abnormality and the incidence in a control series is considered significant only if it could occur by chance no more than once in 80 times, i.e., Deviation ÷ Standard Deviation equals 2.5 or more.

†On the basis of the pathologic examination of 1,000 abortuses, Hertig¹⁶ has postulated a theoretically possible salvage rate of 60 per cent, assuming that 40 per cent of these would carry regardless of treatment. The higher salvage in these 219 patients who received stilbestrol suggests that perhaps Hertig placed the spontaneous cure rate too low. If the spontaneous cure rate is placed at 50 per cent, the highest figure reported, then the theoretically possible salvage rate becomes 70 per cent on the basis of Hertig's observations. A 78 per cent salvage in 219 cases is not significantly greater than 70 per cent.

utilization of C.G. An important part of the understanding of this concept is the realization that stilbestrol is given not because it is estrogenic but because it stimulates the secretion of estrogen and progesterone. The dosages prescribed are not enough per se to raise the estrogen level above the physiologic norm of pregnancy (v.i.). It may be assumed, therefore, that any effect that stilbestrol has in these dosages is through its ability to stimulate a greater production of the placental steroid hormones rather than through its estrogenic activity.

Indications for Stilbestrol Therapy in Pregnancy

If the above concept is correct stilbestrol should prove beneficial in any abnormal situation of pregnancy in which progesterone deficiency may be etiologically involved, *provided the cells which secrete the steroid hormones are still capable of functioning.* That progesterone deficiency might result in abortion, miscarriage, and premature delivery has been assumed since 1929, when the classical investigations of Corner and Allen on the physiologic properties of the corpus luteum hormone were published.¹³ That a progressive deficiency of the steroid hormones invariably precedes the onset of late pregnancy toxemia, eclampsia, premature delivery and intrauterine death has been shown by the investigations of Smith and Smith.⁵ It has been repeatedly pointed out by them, moreover, that a reciprocal relationship exists between the vascular supply to the placenta and the circulating level of steroid hormones, adequate vascularity being essential for the normal production and metabolism of estrogen and progesterone and adequate hormonal supply being equally essential for vascular development in the pregnant uterus. On this basis, they have never felt that the primary abnormality responsible for late pregnancy complications was necessarily hormonal, but they are of the opinion that this deficiency is always a contributory factor to the final syndrome which precipitates the clinical manifestations.¹⁴ By combating this hormonal deficiency it was hoped that stilbestrol, even in such conditions as essential hypertension and twin pregnancy where the primary deficiency is almost certainly of maternal vascular origin rather than hormonal, would postpone the onset, lessen the severity, and possibly reduce the incidence of later pregnancy complications. The use of stilbestrol alone as a definitive measure for the treatment of late pregnancy toxemia, as opposed to its prophylactic use, is not recommended by them because of their evidence that the onset of clinical signs reflects syneptial degeneration, toxin formation, and vascular damage so advanced that increased secretion of progesterone cannot be stimulated.¹²

Dosage

The dosage schedule proposed by the Smiths, and which has been followed by most of the obstetricians who contributed to the present study, is based upon their quantitative determinations of hormonal levels throughout normal pregnancy, and is planned to approximate physiologic conditions as closely as possible.* Five milligrams daily by mouth is started during the sixth or seventh week (counting from the start of the last menstrual period). The daily

*The average daily estrogen excretion of women during normal pregnancy, if expressed in milligrams of estradiol plus estrone plus estriol, has been found to increase from about 0.5 mg. at eight to twelve weeks to 40 mg. at thirty-eight weeks. At thirty-six weeks, when we advise the cessation of stilbestrol therapy, the average excretion is about 15 to 20 mg. Recovery experiments in women have indicated that no more than 10 per cent of administered estrogen is excreted early in pregnancy and no more than 15 per cent during the last trimester. Excretion, therefore, may be assumed to represent about these percentages of the amount originally formed. Our dosage schedule of 5 mg. of stilbestrol at six or seven weeks increasing to 125 mg. during the thirty-sixth week, therefore, should approximate the average level of production. This means that the level of circulating estrogens in an average normal woman (assuming that all the stilbestrol taken orally was absorbed) might conceivably be doubled. Even if such complete absorption occurred, which is unlikely, the level of estrogen of any patient on our schedule would still be within the range of normal, since there is such a wide variation in normal women.

after three, however, is only 16.4 per cent, and if the same calculations are carried to four and five successive abortions, the spontaneous cure rate becomes 2 and 0.5 per cent, respectively. The results reported in Table III, therefore, cannot possibly be ascribed to chance, and seem to establish beyond any reasonable doubt the value of stilbestrol therapy in habitual abortion. It is to be remembered that only 15 per cent of these patients had threatened to abort when therapy was started, and comparison of the figures in Tables I and II indicates, as would be expected, that prophylactic treatment gives better results. Furthermore, many of these chronic aborters were given small doses of stilbestrol during the cycle of conception, as recommended by Smith,²⁰ for the purpose of stimulating better luteal secretion and thereby providing a more normal maternal environment from the very start. It is theoretically possible that a certain percentage of pathologic ova were averted by this means. In many of these patients the previous abortuses had been found defective.

TABLE III. STILBESTROL FOR CHRONIC ABORTION; REPEATED CONSECUTIVE ABORTIONS PRECEDING THERAPY; NO SUPPLEMENTARY THERAPY—127 CASES*

| PREVIOUS ABORTIONS | NO. OF CASES | CARRIED TO 28 WK. (PER CENT) | | LIVING AND WELL BABIES (PER CENT) | |
|-----------------------|--------------|---------------------------------|----|--------------------------------------|----|
| 2 | 67 | 56 | 84 | 54 | 81 |
| 3 | 38 | 33 | 87 | 33 | 87 |
| 4 | 17 | 11 | 65 | 10 | 59 |
| 5 | 5 | 2 | 40 | 1 | 20 |
| Total | 127 | 102 | 80 | 98 | 77 |

*Also included in Tables I and II. One hundred had no living children. Twenty-four were treated for threatened abortion; the rest prophylactically. Many (? exact number) took stilbestrol (0.1 to 0.3 mg. daily) during cycle of conception.

Effects of Variation in the Dosage Schedule.—Of the 18 women (Tables I and II) whose dosage of stilbestrol was considerably below that recommended, only 50 per cent carried. Of the 28 women who were given what we would consider an overdosage only 17, or 61 per cent, carried. Both of these figures are significantly below that for the group as a whole (i.e., 80 per cent of the 491 patients treated for abortion). We have considered the dosage too high if 10 mg. or more are given daily for more than 10 consecutive days before the sixth week, 25 mg. or more daily before the tenth week, 50 mg. or more before the fifteenth week, and 100 mg. or more before the twentieth week. Although most of the doctors, in treating abortion, followed the Smith and Smith schedule fairly closely up to the twentieth week, many of them felt that the full dosage was not necessary once the danger period had been passed. The effect of these variations upon later pregnancy are summarized in Table IV. All of the 99 women listed in column 2 continued to take stilbestrol through the thirty-fifth week, but the weekly increase was discontinued late in the second trimester, and in some instances the dosage was decreased by 5 mg. at weekly intervals after the twenty-fifth week, so that the final dose during the thirty-fifth week was 25 mg. instead of 125 mg. daily. These patients did as well during the third trimester as did the patients on the full Smith and Smith schedule (column 1) except for a somewhat higher incidence of late pregnancy toxemia. The incidence of premature delivery was more than doubled when stilbestrol was entirely discontinued at twenty-five to thirty-four weeks (column 3), although the fetal loss was still only 5 per cent. When it was stopped at twenty to twenty-five weeks (column 4) there was an even more marked increase in the incidence of premature delivery, a 12 per cent fetal loss due to prematurity and a considerable increase in the incidence of late pregnancy toxemia. We very much doubt if the premature deliveries in these cases were directly

worthy that the least impressive salvage rate (74 per cent) was in the group of threatened aborters who had had no previous abortions. A possible explanation for this is that these patients were less alarmed about their symptoms and therefore less prompt in reporting to their obstetricians and starting upon stilbestrol therapy.

Stilbestrol for Abortion: Prophylactically on the Basis of Past History.—(Table II.) Forty-one patients were treated because they had been sterile for two to ten years previously. Six of these aborted, and there was an additional fetal loss from premature delivery. Although the incidence of abortion is said to be somewhat increased in pregnancy following a period of infertility, there is no general agreement as to the validity of this statement. We cannot evaluate the results in these patients, but include them for what they may be worth. The same may be said for the group of 16 patients who were treated for surgical reasons, including fibroid uterus, previous operations on ovaries, uterus, or cervix, or operations during early pregnancy. Of the 272 women treated prophylactically, 215 were given stilbestrol because of a history of previous abortions. One hundred thirty-five had had two or more previous abortions, with an average of 2.8 per patient. One hundred five of these, 78 per cent, carried to twenty-eight weeks, and 72 per cent obtained living children. These figures compare favorably with those reported by Vaux and Rakoff in 24 women whose previous pregnancies averaged 2.9 abortions per patient and who were treated with estrogen and progesterone.¹⁷ If the Smith and Smith concept is correct, stilbestrol administration should give better results than could be acquired by substitution therapy with progesterone alone or with estrogen plus progesterone (provided the cells which secrete the hormones are capable of responding to stimulation), since secreted hormones would be supplied at a more physiologic level and a more uniform rate than could be accomplished by parenteral administration.

TABLE II. STILBESTROL FOR ABORTION PROPHYLACTICALLY (ON BASIS OF PAST HISTORY)
272 CASES*

| INDICATION FOR THERAPY | * NO. OF CASES | CARRIED TO 28 WEEKS (PER CENT) | LIVING AND WELL BABIES (PER CENT) |
|----------------------------|----------------|--------------------------------------|---|
| Infertility (2 to 10 yrs.) | 41 | 86 | 82 |
| Surgical reasons | 16 | 81 | 75 |
| Previous abortions | | | |
| 1 | 80 | 87 | 83 |
| 2 | 65 | 82 | 77 |
| 3 | 41 | 87 | 80 |
| 4 or more | 29 | 67 | 52 |
| Total | 272 | 83 | 78 |

*Including 9 cases on too low dosage, 3 of whom aborted, and 13 cases on too high dosage, 7 of whom aborted.

Abortion Sequences.—(Table III.) Of the 434 patients treated either definitively or prophylactically for abortion, 127 had had two to five consecutive abortions prior to the pregnancy in which stilbestrol was administered. Malpas,¹⁸ on the basis of the known incidence of abortion in the British Empire and of the accidental and recurrent factors involved, has calculated that a woman who has aborted two recurrent gestations has a 62 per cent chance of carrying the following pregnancy, whereas if she has aborted three successive previous pregnancies her chance of carrying a fourth is reduced to 27 per cent. Eastman,¹⁹ applying the same mode of calculation to the statistical analysis of abortions by American authors, arrived at approximately the same figure for those with a history of two previous abortions. His spontaneous cure rate

activity of this organ. No cases in this series were given significantly larger dosages during later pregnancy than those recommended by us, but 28 patients received what we consider overdosage prior to the twentieth week. Seventeen carried to the twenty-eighth week (Table IV, column 6). Despite the continued administration of stilbestrol, over one-half of them developed later pregnancy complications with the loss of three of the 17 babies. This is a small group but the fetal loss is significantly greater than when the amounts recommended were given and the results are sufficiently alarming to convince us of the real danger of overdosage, especially during the early weeks when the placenta is assuming ovarian function in the matter of hormone production.*

TABLE IV. STILBESTROL FOR ABORTION; EFFECT OF DOSAGE UPON LATER PREGNANCY OF 491 PATIENTS TREATED DEFINITELY OR PROPHYLACTICALLY.
393 (80 PER CENT) CARRIED TO 28 WEEKS

| DOSAGE { WEEKS | (1) S & S 7-36 | (2) <S & S AFTER 20 | (3) STOPPED @ 25-34 | (4) STOPPED @ 20-25 | (5) TOO LOW THROUGH- OUT | (6) TOO HIGH 4-20 |
|---------------------|----------------------|---------------------------|---------------------------|---------------------------|-----------------------------------|-------------------------|
| | No. of cases | | | | | |
| Premature > 3 wks. | 213 | 99 | 19 | 34 | 9 | 17 |
| Baby lived | 8.8% | 7.1% | 21.0% | 18.0% | 22.0% | 30.0% |
| Baby died | 4.5% | 4.0% | 5.2% | 12.0% | 11.0% | 12.0% |
| Toxemia | | | | | | |
| Baby lived | 1.8% | 3.0% | 0 | 8.8% | 0 | 6.0% |
| Baby died | 0 | 1.0% | 0 | 0 | 0 | 6.0% |
| Total fetal loss | 4.5% | 5.0% | 5.0% | 12.0% | 11.0% | 18.0% |
| Total complications | 15% | 15% | 26% | 39% | 33% | 54% |

Stilbestrol Prophylactically Against Complications of Late Pregnancy.—In presenting the data concerning 95 patients who were given stilbestrol because of a history of late pregnancy complications, we have first summarized the total results comparing the outcome of the treated pregnancies of the group with the past obstetrical histories of these same patients (Table V). Since only 18 of their 197 previous pregnancies had been normal throughout, there were 179 abnormal pregnancies in their past histories or an average of 1.9 per patient. With such a low average incidence of previous trouble the significance of the apparent reduction, in this pregnancy on stilbestrol, in loss of the fetus from abortion, prematurity, stillbirth, and pre-eclampsia might be questioned. In the lower part of Table V, however, we have grouped these patients according to the number of previous complications that constituted the indication for stilbestrol administration. All of the complications listed are associated, we have reason to believe, with a deficiency of progesterone. If a patient has three or more pregnancies in each of which one or another of these abnormalities recurs, an inherent inadequacy may well be involved and the expectancy of a normal outcome in any succeeding pregnancy greatly reduced. In these patients a comparison of their past histories with the outcome of this pregnancy on stilbestrol would seem to be valid. There were 22 such patients. Eighty-three, or 92 per cent, of their previous 91 pregnancies were complicated by one or another of the abnormal conditions listed, and only 31, or 35 per cent, resulted in living infants. On stilbestrol these 22 patients had an incidence of 64 per cent pregnancy complications and 16, or 73 per cent, obtained living

*Davis and Fugo²¹ administered 50 to 200 mg. of stilbestrol daily for six to eight weeks to fifteen women between the fourth and sixteenth weeks of pregnancy, and observed no increase in pregnanediol excretion. Their published data actually reveals a decrease in urinary pregnanediol after eight to nineteen days of these very large doses. This is particularly significant, since pregnanediol excretion normally increases quite rapidly at this time. All but eight of their cases had therapeutic abortions. One of these eight had a miscarriage during the second trimester. No details were given as to the course or outcome of the other pregnancies.

due to estrogen withdrawal since the interruption of pregnancy by this means has been tried at various stages of gestation without effect. It seems more likely that many of these patients who were primarily treated for abortion had an inherent deficiency in their ability to secrete the steroid hormones which still prevailed after their usual danger period had passed and that they required the extra stimulation supplied by stilbestrol in order to carry normally to term. In Fig. 1 are presented our findings on the pregnanediol excretion of one of these patients in whom we investigated the effect of reducing the dosage of stilbestrol after her usual danger period had passed. The results indicate that in this particular patient stilbestrol in adequate amounts throughout was essential for the continued increase in pregnanediol excretion that characterizes normal pregnancy.

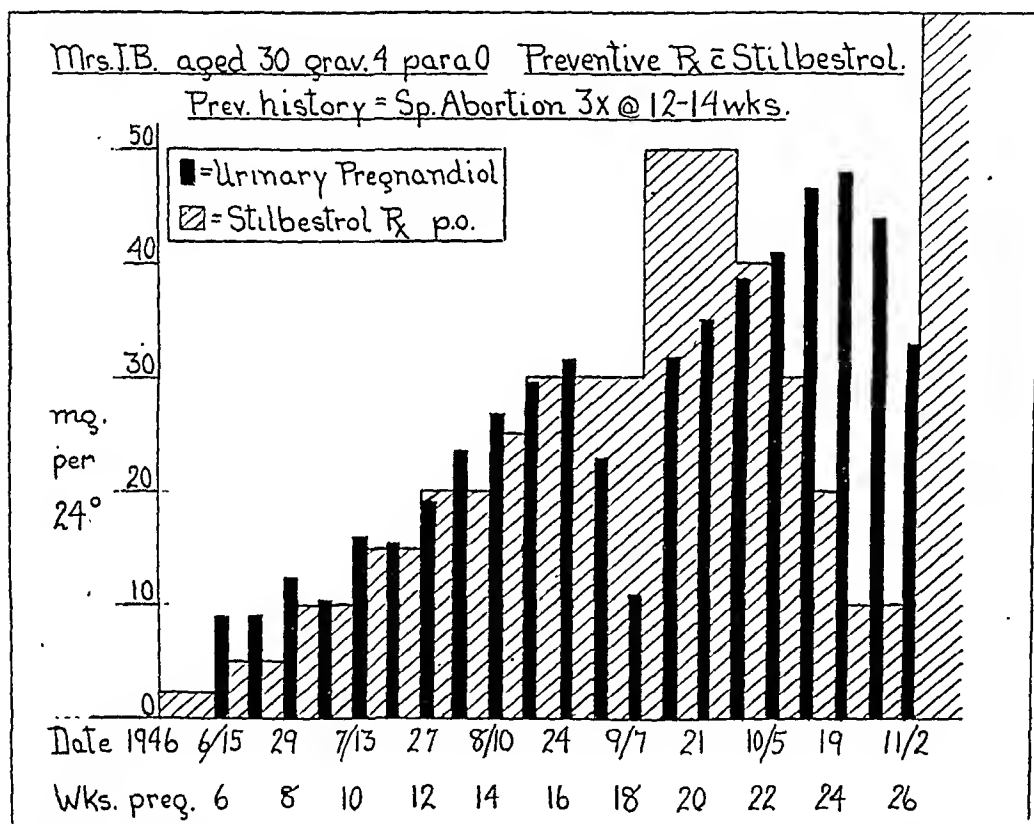


Fig. 1.—Effect upon pregnanediol excretion of two attempts to give less than the prescribed amount of stilbestrol after the patient's usual danger period had passed.

During the sixteenth and seventeenth weeks the dosage was maintained at 30 mg. instead of the usual increase of 5 mg. daily at weekly intervals. Starting at twenty-one weeks the dosage was decreased by 10 mg. daily at weekly intervals in place of the usual increase. At twenty-six weeks the dosage was increased to 75 mg. daily where it was maintained through the thirty-sixth week. She went into labor spontaneously two days after the cessation of therapy. A healthy baby (6 lbs. 2 oz.) was delivered by cesarean section and survived.

We have been concerned about the theoretical dangers of stilbestrol over-dosage. It is well known that estrogens in unphysiologic amounts are toxic to the fetuses of rodents. It has long been known, also, that the prolonged administration of large amounts of estrogen depresses the gonadotropic activity of the pituitary. Similarly, it seems likely that the continued administration of unphysiologic doses of stilbestrol during pregnancy might inhibit the placental secretion of steroid hormones and even do permanent damage to the secretory

TABLE VI. STILBESTROL PROPHYLACTICALLY FOR PREMATURE DELIVERY; 46 PATIENTS* WHOSE PAST HISTORIES CONTAIN NO DELIVERIES LATER THAN 36 WEEKS. NO SUPPLEMENTARY THERAPY.

| PAST OBSTETRICAL HISTORIES | | | | | | THIS PREGNANCY ON STILBESTROL | | | | | | |
|--------------------------------------|--------------------------------|---------|-----------|------------|---------------------|-------------------------------|--------------------|-----------|-------------------|----|---------------------|----|
| PREVIOUS PREM. DELIV- ERIES | TOTAL PREG- NAN- CIES | ABORTED | PREMATURE | | TOTAL L & W % | NO. OF CASES | TERM DELIVERIES | PREMATURE | | | TOTAL L & W % | |
| | | | NO. | L & W % | | | | NO. | BABIES L & W % | | | |
| 1 | 19 | 0 | 19 | 10 | 10 | 19 | 9 | 47 | 10 | 6 | 60 | 79 |
| 2 | 30 | 1 | 29 | 31 | 29 | 15 | 5 | 33 | 10 | 5 | 50 | 67 |
| 3 | 21 | 5 | 16 | 0 | 0 | 7 | 3 | 43 | 4 | 1 | 25 | 57 |
| 4 or more | 23 | 3 | 20 | 35 | 30 | 5 | 2 | 40 | 3 | 1 | 33 | 60 |
| Totals | 93 | 9 | 84 | 21 | 19 | 46 | 19 | 41 | 27 | 13 | 48 | 67 |

*Also included in Table V.

Stilbestrol Prophylactically to Pregnant Women With Known Essential Hypertension.—(Table VII.) It is well known that essential hypertension is a predisposing factor to superimposed late pregnancy toxemia and to premature delivery. Cosgrove²² has placed the fetal loss in all pregnant women with essential hypertension, regardless of severity, as high as 38 per cent. In Table VII are presented the data concerning 17 women who had been under medical care for essential hypertension before they became pregnant. Since hypertension is a progressive disease, any improvement in the outcome of this pregnancy on stilbestrol over their past obstetric histories should be highly significant. This is particularly true, since three of these women taking stilbestrol had the added hazard of carrying twin pregnancies, whereas there had been no twins in the past pregnancies of any of the seventeen cases. There were no primiparas among them, and all had had previous obstetric abnormalities. Of their 45 previous pregnancies only 6, or 13 per cent, had been uncomplicated, and the fetal loss had been 20, or 42 per cent. In this pregnancy on stilbestrol the incidence of uncomplicated pregnancies was nearly tripled, and the fetal loss was only 2, or 12 per cent. The difference between these figures is of unquestionable significance. Actually the fetal loss was only 10 per cent, since 18 out of a possible 20 infants survived. One patient separated her placenta at twenty-four weeks. The other fetal loss was in a severe hypertensive patient (blood pressure 210/110) who had albumin from the start of pregnancy and underwent cesarean section at thirty-one weeks, the infant dying of prematurity. If this patient and another with known nephritis are omitted from the series, the incidence of albuminuria on stilbestrol is only 20 per cent. If a rise in blood pressure during the last two months constitutes a diagnosis of superimposed toxemia in these patients, then seven, or 41 per cent, of the seventeen pregnancies treated had this complication. The difference between this figure and the 69 per cent incidence of increased blood pressure in their previous pregnancies is statistically significant. The only patients of this series who had any supplementary therapy were two who were on a rice diet. Both had superimposed toxemia and cesarean section before term, one of them being the patient mentioned above whose baby died of prematurity. None of the other pregnancies was artificially interrupted.

Although this is a small series of cases, the results seem sufficiently encouraging to warrant further trials of this therapy in dealing with hypertension complicating pregnancy. There is no known reason to suppose that stilbestrol could influence the disease itself or control the hypertension beyond the possibility of keeping it within the nonpregnant range, but it may well postpone the onset and reduce the severity of obstetric complications and thereby increase the fetal salvage by combating the progressive deficiency of estrogen and proges-

children. The difference between these figures is strikingly significant. These results, although not conclusive, indicate that stilbestrol therapy for such patients may be expected to increase their chances for a normal pregnancy and a living child.

TABLE V. STILBESTROL PROPHYLACTICALLY FOR COMPLICATIONS OF LATE PREGNANCY (ON BASIS OF PAST OBSTETRIC HISTORY), 95 CASES

| | PAST HISTORY | | ON STILBESTROL | |
|--------------------------|--------------|-----|----------------|-----|
| No of pregnancies | 197 | | 95 | |
| Abortions (< 22 wks.) | 20 | 10% | 3 | 3% |
| Premature (< 37 wks.) | 84 | 43% | 31 | 33% |
| died of prematurity | 60 | 30% | 11 | 12% |
| Stillborn (? cause) | 28 | 14% | 4 | 4% |
| Pre-eclampsia | 47 | 24% | 12 | 13% |
| Pre-eclampsia, baby died | 22 | 11% | 3 | 3% |
| No complications | 18 | 9% | 45 | 47% |
| Total living babies | 67 | 34% | 71 | 75% |

Of the 95 cases on stilbestrol:

| INDICATION FOR R | PAST OBSTETRIC HISTORY | | | THIS PREGNANCY ON STILBESTROL | | |
|------------------|------------------------|----------|--------------|-------------------------------|----------|--------------|
| | TOTAL PREG-NANCIES | ABNORMAL | BABIES L & W | TOTAL PREG-NANCIES | ABNORMAL | BABIES L & W |
| 1 | 54 | 87% | 37% | 47 | 53% | 75% |
| 2 | 52 | 100% | 30% | 26 | 42% | 77% |
| 3 or more | 91 | 92% | 35% | 22 | 64% | 73% |

Stilbestrol Prophylactically for Premature Delivery.—(Table VI.) Forty-six of the patients prophylactically treated for late pregnancy complications were given stilbestrol in the hope of combating their tendency towards premature delivery. The recurrent nature of this abnormality is well recognized. Of their 93 previous pregnancies, there had been none that were carried beyond the thirty-sixth week, nine having aborted and 66 having been lost because of prematurity, making a total of only 18 living babies, or 19 per cent. About 40 per cent of them carried to term on stilbestrol. Although this is a considerable improvement over their previous histories of no term deliveries, the fact that the percentage of term deliveries on stilbestrol was uniform, regardless of the number of previous premature deliveries, suggests that in more than one-half of these cases, factors other than hormonal are predominantly involved. The fetal salvage, however, was more than tripled, even among the 12 patients who had had three or more previous early deliveries. This was in part due to the fact that most of them carried longer than in previous pregnancies, but not entirely. Several of the obstetricians noted that the placentas from stilbestrol treated patients were grossly more healthy looking and the babies unusually rugged for their gestational age. It would appear, therefore, that stilbestrol administration to these patients who repeatedly deliver early not only reduces the incidence of premature delivery, but considerably increases their chances of obtaining a living child. Our explanation would be that although the progressive deficiency of steroid hormones which invariably, according to our findings, precedes labor whether at term or prematurely, may, in most of these cases, be an end result of some more primary condition, it is still a contributory factor. By combating it the onset of labor may be postponed, but perhaps of even more importance is an increased vascularity from a higher level of estrogen and progesterone secretion, thereby providing a better maternal environment for the fetus so that when delivery does occur it is in better condition than it would have been if stilbestrol had not been given.

The Use of Stilbestrol for the Definitive Treatment of Late Pregnancy Complications.—We have shown that stilbestrol administration alone as a definitive measure in late pregnancy toxemia is fruitless,¹² and we have not recommended its use in any complication of late pregnancy except as preventive therapy. Our reason for this has been the conviction that the onset of clinical signs in later pregnancy reflects a premature senility of the placenta which has already progressed to a degree that cannot be influenced by hormone administration alone. Twenty-four patients of this series, however, were so treated. Two of them, who were started on stilbestrol late in the second trimester because of the development of toxic signs, showed progressive toxemia during stilbestrol administration. The pregnancy had to be interrupted at twenty-six weeks in one of them, and the other had a stillbirth at thirty-two weeks. Twelve other patients were given stilbestrol for bleeding between weeks twenty-three and thirty-two. Three of these carried to term, but in one the only symptom was slight spotting for one day only, and the amount of stilbestrol given was too little conceivably to have influenced placental secretion. Three had premature babies that survived. One of these had a viable infant when bleeding began, and delivered spontaneously after only three days of stilbestrol administration. The pregnancy of each of the other six bleeding patients of this group terminated in spontaneous premature delivery with death of the infant.

Ten other patients were given stilbestrol because of uterine contractions with no show between weeks twenty-one and twenty-nine. Although eight of these carried to term and nine of them obtained living children, we cannot conclude that the administered stilbestrol was responsible, first, because so many patients normally carry to term after such episodes and, second, because half of these cases were given stilbestrol in such low dosages that it seems improbable that it could have had any effect.

It is, of course, conceivable that abnormal bleeding in later pregnancy might in some cases be due to local placental site pathology rather than to generalized placental senility of syncytial trophoblastic origin with its concomitant irreversible deficiency of sex steroids. In such cases stilbestrol administration might help and may have contributed to four of the six successful outcomes in the twelve patients of this series treated definitively for bleeding after the twenty-second week. It could certainly do no harm, but it seems likely that the usual obstetric measures and bed rest would be just as effective.

Toxic Manifestations From Stilbestrol.—In the 632 case reports that we have received to date, toxic reactions have been recorded nine times, an incidence of 1.4 per cent. Six of these patients complained of nausea, one of headaches and somnolence, one of vaginal discharge, and one of a skin rash. Four of them discontinued therapy, three with relief of symptoms and one without. The other five continued on the regular schedule and their symptoms disappeared. Whether or not such symptoms are due to the stilbestrol, it is probably only the rare case that will not be able to tolerate the full dosage schedule throughout with only temporary discomfort. For such a patient the amounts recommended may actually constitute overdosage, and the dosage given should be regulated just below the amount that brings on symptoms. A few patients, in whom therapy had been discontinued after their danger periods had passed, voluntarily began taking stilbestrol again because they claimed that they felt so much better when taking it.

Summary

The basis for the use of stilbestrol in pregnancy is briefly reviewed, together with the indications and the dosage schedule recommended. Complete

terone, which we believe in these cases results from vascular deficiency and which is, according to our findings, a contributory factor in all of these accidents of later pregnancy.

TABLE VII. STILBESTROL PROPHYLACTICALLY TO PREGNANT WOMEN WITH KNOWN ESSENTIAL HYPERTENSION; 17 CASES*

| | AVERAGE AGE = 33 YEARS | | RANGE = 22-42 YEARS | |
|-----------------------------------|------------------------|------|---------------------|-----|
| | PAST HISTORY | | ON STILBESTROL | |
| No. of pregnancies | 45 | | 17 | |
| Abortions < 22 wks. | 10 | 22% | 0 | |
| Premature < 37 wks. | 17 | 38% | 5 | 29% |
| Stillborn (? cause) | 2 | 4.5% | 0 | |
| Superimposed toxemia | | | | |
| Rise in B.P. during last 2 months | 31 | 69% | 7 | 41% |
| Albuminuria during last 2 months | 22 | 49% | 5† | 29% |
| No complications | 6 | 13% | 8 | 47% |
| Total fetal loss | 20 | 42% | 2 | 12% |

*Including three twin pregnancies; ∴ 18 of 20 babies lived. Two of the 17 were on rice diet. Both had rise in blood pressure and albuminuria. One of these babies died.

†Including two who had albuminuria throughout pregnancy (one a known nephritic).

Stilbestrol Prophylactically to Pregnant Women with Diabetes.—Although much of our investigative work on the complications of late pregnancy has been done in diabetic women, only nine of the present series had this disease. Two other patients whose pregnancies were complicated by diabetes and who were treated with stilbestrol were reported by us,^{11, 12} making a total of only eleven cases to date. The diabetes of all was classified as severe. Three patients were primiparous. (These are not included in Table V.) The other eight were patients who had all had obstetrical complications in previous pregnancies. Twelve of the thirteen previous pregnancies since the onset of diabetes had been complicated by toxemia, intrauterine death or premature delivery. Only two of these thirteen pregnancies had resulted in living children. There were three fetal deaths in this series of 11 patients treated with stilbestrol but only one of these, due to spontaneous delivery at twenty-six weeks, could be considered a failure so far as stilbestrol therapy is concerned. Another was due to placenta previa, and the third was that of the baby of an Rh-negative patient who was induced at thirty-seven weeks because of a rising anti Rh titer. She had a prolonged labor, and a Braxton-Hicks delivery was performed, the infant being hydrocephalic. (There has been only one other congenital anomaly in this whole series of patients given stilbestrol, an infant with webbed fingers.) There was no toxemia in these 11 diabetic women, although 6 of them were allowed to carry to term. Three babies were described as unusually large and edematous. All three did well but their occurrence in uncomplicated pregnancies substantiates our early observation that there seems to be no connection between the large infants of diabetic mothers and the hormonal imbalance which so consistently accompanies toxemia, premature delivery and intrauterine death in both diabetic and nondiabetic women.²³

Eleven cases are too few to warrant any conclusions concerning the value of stilbestrol as a preventive measure in pregnancy complicated by diabetes. It seems reasonable to assume, however, that the results would be as good as when it is used prophylactically for the same complications in nondiabetic women, since the same premature deficiency of estrogen and progesterone prevails. We are hoping that our dosage schedule will be given a more extensive trial in diabetic clinics. It is certainly a less expensive form of treatment and should be more successful than the attempt at replacement therapy with estrogen and progesterone originally proposed by us^{2, 24} and favorably reported upon by White.²⁵

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case reports on 632 pregnant women, to whom diethylstilbestrol was given largely for the indications and in the amounts recommended by us, have been analyzed. They have been divided according to the indications for therapy, i.e., threatened abortion (219 cases), abortion prophylaxis (272 cases) and prophylaxis against late pregnancy toxemia, intrauterine death, and premature delivery (98 cases). Although we have not recommended stilbestrol as a definitive measure in later pregnancy, 24 patients were so treated and are considered separately. Nineteen cases that fell into none of these categories are omitted.

Seventy-eight per cent of the patients who were treated for bleeding between the sixth and twenty-first weeks carried to twenty-eight weeks, and 72 per cent had living and well babies. The highest spontaneous cure rate reported in the literature is 50 per cent. Eighty-three per cent of the patients who were given stilbestrol prophylactically against abortion carried to twenty-eight weeks, and 78 per cent had living and well babies. In the 127 cases who had had two to five consecutive abortions prior to the one in which stilbestrol was given, the fetal salvage averaged 77 per cent. In each group it was very significantly higher than the spontaneous cure rate as established by Malpas and Eastman. In the total 491 cases treated for abortion the incidence of abortion and of later pregnancy complications was higher when the dosage schedule was not followed than it was in the group as a whole.

In many of the patients treated prophylactically for late pregnancy complications it was impossible to evaluate the effect of stilbestrol therapy, and this part of our report must be considered preliminary. Twenty-two of them, however, had had three or more previous obstetric abnormalities, 27 had had two or more premature deliveries, 17 had known essential hypertension with bad obstetric histories, and nine had diabetes, six of these with bad obstetric histories. Considering the past obstetric histories of these patients, the course and outcome on stilbestrol gave good indication that the administration of this drug as a preventive measure may be expected to reduce the incidence of those complications of later pregnancy associated with a premature deficiency of the placental steroid hormones, estrogen and progesterone. There was even stronger evidence that the onset of these complications would be postponed and the fetal mortality reduced. The results of the use of stilbestrol as a definitive measure in later pregnancy were not promising.

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Following an eight-hour fast, intravenous fluids, consisting of 5 per cent glucose in distilled water, were administered at a constant rate (6 to 8 ml. per min.) from 6 A.M. until completion of the test. Urine specimens were collected by catheter each half hour until three specimens of approximately equal amount were obtained. The third specimen served as the control period (Cl-1). The patient's hand or foot was then immersed to the wrist (or ankle) in an ice water bath maintained at a temperature of 1° C. for a fifteen-minute period; and urine specimens were collected after completion of this immersion (Cl-2), after the succeeding fifteen minutes (Cl-3), and upon completion of a final one-half hour collection (Cl-4). Blood pressure, pulse, respirations, and fetal heart rate were obtained at regular intervals. Urine chlorides and urine proteins were estimated by the usual methods. Urine specific gravity was obtained gravimetrically using 2 ml. pyknometer bottles, a suitable correction being made for the protein content.

Results

1. *Rate of Urine Flow.*—Data are divided into two groups: (1) Cases having no significant change, or even an increase in minute volume as a result of ice immersion; and (2), those having a diminished urine excretion (Figs. 1 and 2). In this latter group, following a control period (Cl-1), the minute volume dropped sharply during ice immersion (Cl-2), although the antidiuretic effect was often more pronounced during the succeeding fifteen minutes (Cl-3). The rate of flow during Cl-4 tended to return to that of Cl-1. Three-fourths of the patients subjected to the test had this suppression. The mean and maximum rise in systolic and diastolic blood pressure was slightly more in those showing a decreased excretion than in those without. The reaction was non-specific in that pregnancy toxemia occurred in both groups. In general, patients experiencing great discomfort from immersion had a urine suppression. A fifteen-minute episode of anuria occurred in one pre-eclamptic case (Figs. 3 and 4).

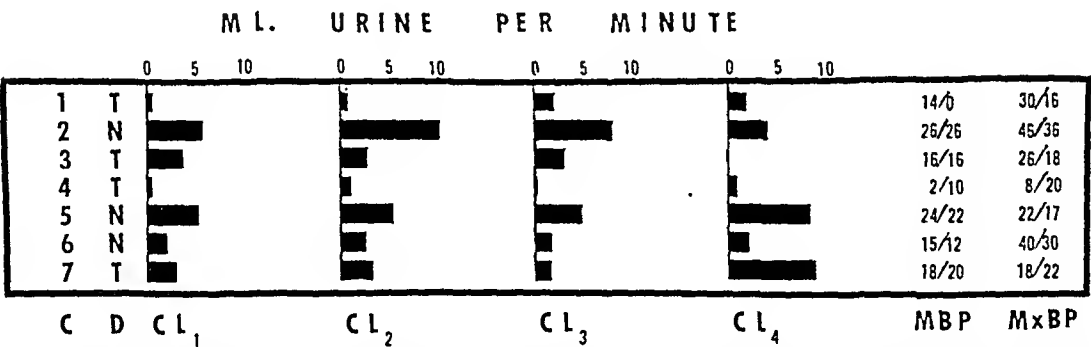


Fig. 1.—Renal response to thermal stimulus. Cases without urine suppression. C = Case number. D = Diagnosis: T - Toxemia of pregnancy, N - Normal pregnancy; Cl-1 to 4 = Consecutive clearance periods; MBP = Mean blood pressure change, mm. Hg; MxBP = Maximum blood pressure change, mm. Hg. Immersion in ice water bath during second (Cl-2) clearance period.

2. *Proteinuria.*—Findings are plotted graphically (Fig. 5). These illustrate a slight trend toward an increased excretion per minute of protein during and following ice immersion. But comparison of numbers in Fig. 5 with Figs. 1 and 2 discloses that degrees of change in blood pressure do not necessarily correlate with the amounts of protein excreted. It is difficult to reconcile such findings with those of Chesley et al,² who noted a direct relationship between an increase in proteinuria and the degree of rise in blood pressure, and who ob-

RENAL RESPONSE TO THERMAL STIMULUS*†

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APPARENTLY several kinds of environmental stimuli will cause an elevation of blood pressure. Among these are exposure to cold or irritant gases, pain, situations disturbing the emotions, breath holding, muscular activity, and sudden changes in gravity. Extreme degrees of lability following such stimuli have been interpreted as evidence of a prehypertensive state.¹ Thus, various "tests" have been devised, principally to standardize the stimulus employed.

The most commonly used method for determining vascular lability employs exposure to cold. Ordinarily the subject's hand is plunged into ice water to the wrist for one minute, blood pressure changes being recorded before, during, and following this experience.¹

It is reasonable to suppose that any such experience violently affecting blood pressure might also alter other body functions. Chesley et al² reported an increased proteinuria immediately following the "cold test." Dieckmann and Michel³ noted various untoward symptoms and signs following immersion; these included persistent hypertension, blurred vision, epigastric pain, hematuria, and two instances of vascular collapse. Paroxysmal cold hemoglobinuria is found sporadically, and Tottermann⁴ observed two instances in which convulsions were precipitated by cold exposure. Ariel et al⁵ found anuria in rabbits subjected to temperatures of 3° C. for periods up to forty-eight hours. Garai,⁶ using the standard cold test, noted an increased response in shipwrecked sailors, these men having been previously exposed to immersion in arctic waters. And Horvath et al⁷ studied Army volunteers under conditions of extreme cold and found a progressive increase in basal metabolic rate.‡

It has been noted previously that the urine volume per minute and urea clearance rate are suppressed following a prolonged cold test.⁸ The present study reports findings following a fifteen-minute immersion of one hand, or foot, in an ice-water bath at a temperature of 1° C. An increased secretion of posterior pituitary substances is suggested as a contributory cause for this phenomenon.

Materials and Methods

A total of 66 patients were used. These included 22 with toxemia of pregnancy, 33 during normal pregnancy, one with diabetes insipidus and pregnancy, one with a glioma of the spinal cord and pregnancy, and nine who were not pregnant. Two of the latter had hypertension or a history of previous toxemia of pregnancy.

*Presented before the Chicago Gynecological Society, Nov. 21, 1947.

†This study was supported in part by the Chicago Lying-in Hospital Fiftieth Anniversary Fund for Research on Eclampsia and Puerperal Fever.

‡For an additional review of this subject see Dieckmann and Michel,³ Chesley et al,² and Garai.⁶

experienced anginal-like symptoms during immersion. The blood pressure in this case rose from 230/130 to 290/195 mm. Hg. Although the hand was kept immersed for only two minutes out of a fifteen-minute clearance period, a marked suppression occurred in the rate of urine excreted.

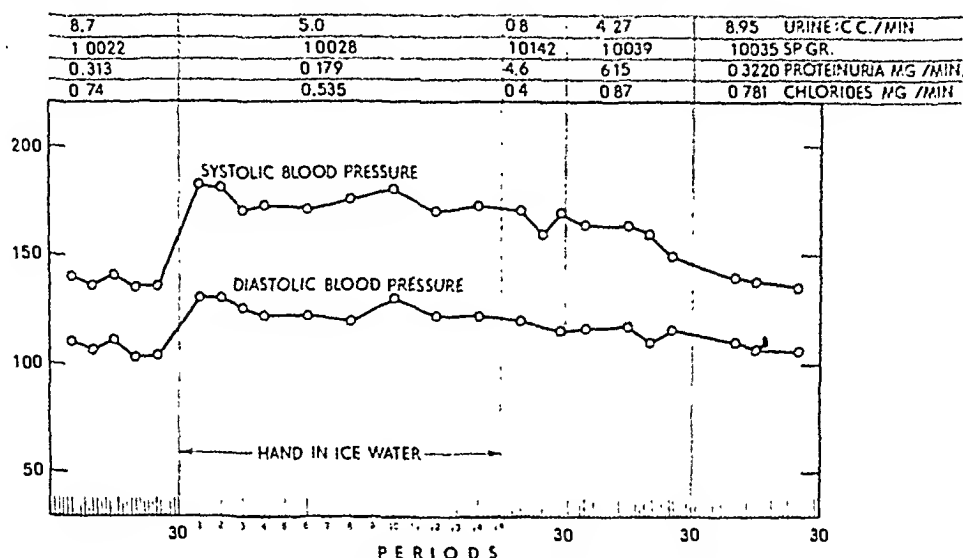


Fig. 3.—Renal response to thermal stimulus. Antepartum eclampsia (M. L. 332886).

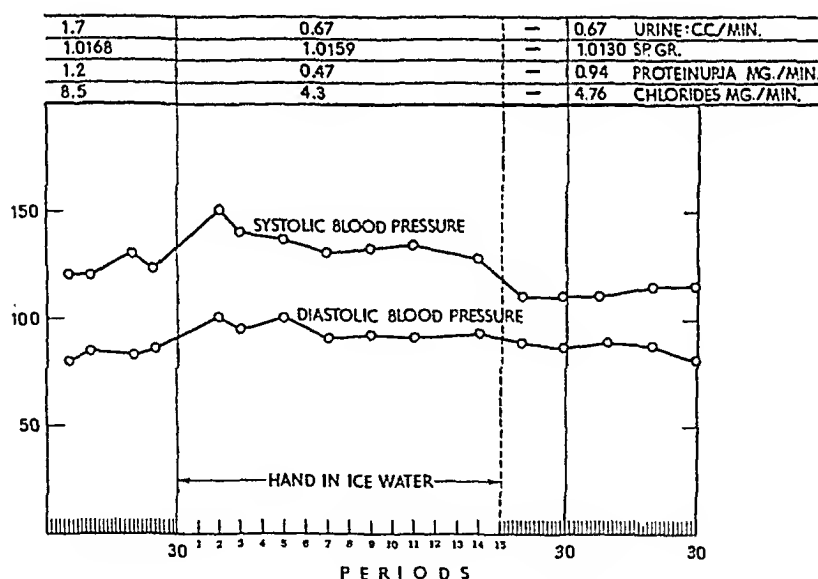


Fig. 4.—Renal response to thermal stimulus. Pre-eclampsia (C. L. 343405).

A slight decrease in pulse and respiratory rate occurred during immersion. The mean fetal heart rate did not vary significantly. Examination of the urine of several subjects disclosed no significant change in cellular constituents per unit of time following the test.

5. *Effect of Anesthesia.*—Patients were tested by immersion of one hand, or one foot, in ice water during ethylene, cyclopropane, or spinal anesthesia. There was no significant rise in blood pressure in these cases. This agrees with Wolff and Hardy¹⁰ who observed that the rise in blood pressure was due to the

served that this proteinuria followed the release of "vasospasm" attending the increased pressure. In some patients in this series the amount of protein excreted/minute actually remained the same or became reduced.

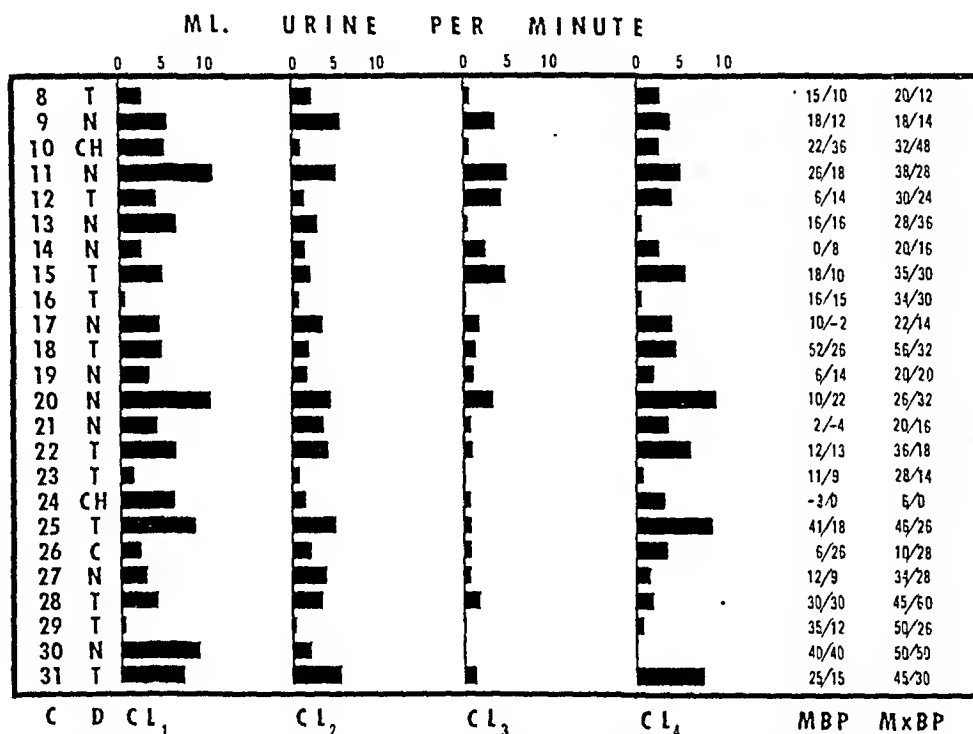


Fig. 2.—Renal response to thermal stimulus. Cases with urine suppression. C = Case number; D = Diagnosis: T - Toxemia of pregnancy, N - Normal pregnancy, CH - Nonpregnant with hypertension, C - Nonpregnant without hypertension; Cl-1 to 4 = Consecutive clearance periods; MBP = Mean blood pressure change, mm. Hg; MxBP = Maximum blood pressure change, mm. Hg. Immersion in ice-water bath during second (Cl-2) clearance period.

3. *Specific Gravity and Chloride Excretion.*—In most instances, as the urine volume lessened during Cl-3, the specific gravity and concentration of chlorides increased (Fig. 6). This is reasonable since specific gravity depends, in part, upon the chloride content of the urine. Reasons for change in the output of chlorides are problematical. The amount of this salt excreted by the kidneys largely depends upon certain extrarenal factors, its plasma concentration, and the rate of its reabsorption, presumably in the distal convoluted tubules;⁹ and this latter factor bears directly to the filtration rate and/or the activity of the posterior pituitary gland.

4. *Blood Pressure, Pulse, Respiration, Fetal Heart Rate, Subjective Symptoms, and Microscopic Examinations of the Urine.*—In most instances the initial sharp rise in blood pressure during immersion was not sustained, but tended to fall gradually as the pain sensation, elicited by the cold, subsided. Although this time interval was variable, it usually lasted four to five minutes in duration. In some patients the blood pressure was even less following cold immersion than previous to it.

In this series all the patients experienced cold and some degree of pain. The latter, usually deep and throbbing, was finally replaced by a sensation of pins and needles, and this was followed by a complete numb adaptation to the stimulus. Several subjects complained of a sharp, cramping epigastric pain which tended to disappear within a few minutes. One (See case 28, Fig. 2)

conscious cold pain elicited by immersion. However, anesthesia, particularly inhalation anesthesia, which obliterates consciousness, may not prevent a urine suppression from immersion. This might become initiated at the site of immersion or as a result of a nerve-conducted reflex to lower centers of the nervous system.

To test this hypothesis four patients were observed under inhalation anesthesia and three under spinal anesthesia. Identical conditions concerning fasting, intravenous fluids, and constant urine excretion were obtained. The foot was used for immersion. Three patients were observed prior to this test without anesthesia, and had a characteristic urine suppression as a result of cold. Inhalation anesthesia was maintained at a stage deep enough to abolish any sensation of pain.

Table I shows the results of patients observed under gas anesthesia. In each case there was a decrease in urine excretion during and following ice immersion. In two instances the blood pressure fell slightly, and in the other two it rose.

TABLE I. EFFECT OF ICE IMMERSION ON URINE EXCRETION DURING ANESTHESIA

| IDENTIFICATION | ANESTHETIC | ML./MIN. | | | | MBP |
|----------------|--------------|----------|------|------|------|---------|
| | | CL-1 | CL-2 | CL-3 | CL-4 | |
| K. B. 158861 | None | 2.6 | 1.7 | 2.5 | 2.7 | 0/8 |
| S. S. 319945 | Ethylene | 0.27 | 0 | 0.53 | 0.47 | -20/-15 |
| | None | 6.7 | 3.0 | 0.54 | 0.6 | 20/22 |
| F. W. 394087 | Ethylene | 1.8 | 1.7 | 0.6 | 1.7 | -5/2 |
| | None | 3.4 | 1.7 | 1.2 | 2.0 | 8/12 |
| P. H. 386325 | Ethylene | 1.46 | 0.4 | 0 | 0.29 | 12/20 |
| | Cyclopropane | 8 | 0.71 | | | 50/30 |

MBP = Mean change in blood pressure.

Immersion in ice-water bath during CL-2

Three patients tested under spinal anesthesia by immersion of one foot in an ice-water bath had no significant change in urine excretion per minute.

Such evidence would indicate that a reflex path exists which is independent of conscious pain but which is abolished by spinal anesthesia, and therefore not initiated locally by some hormonal secretion at the site of immersion. It does not, however, explain whether it is entirely sensory or whether it is of a sensory-endocrine pattern.

The following three cases seem to illustrate this last possibility. The first was a patient with far-advanced cervical carcinoma upon whom a cordotomy, severing the spinal-thalamic tract, had been performed at thoracic 3, above the source of renal innervation. The second case was a patient, near term, with a glioma at cervical 4. Anesthesia of the lower extremities was present in both

TABLE II. EFFECT OF ICE IMMERSION ON URINE EXCRETION IN PRESENCE OF CORD INTERRUPTION

| IDENTIFICATION | DIAGNOSIS | EXTREMITY USED | ML./MIN. | | | | MBP |
|----------------|------------------------|----------------|----------|------|------|------|-------|
| | | | CL-1 | CL-2 | CL-3 | CL-4 | |
| M. K. 250289 | Spinal* cord tumor—C4 | Foot | 4.5 | 6.0 | 4.6 | 4.6 | 0/6 |
| M. D. 352809 | Cordotomy—T-3 | Foot | 5.0 | 4.3 | 4.9 | | 10/0 |
| J. F. 389835 | High spinal ansth.—T-5 | Hand | 1.1 | 1.2 | 0.2 | 0.8 | 10/16 |

MBP = Mean change in blood pressure.

Immersion in ice-water bath during CL-2

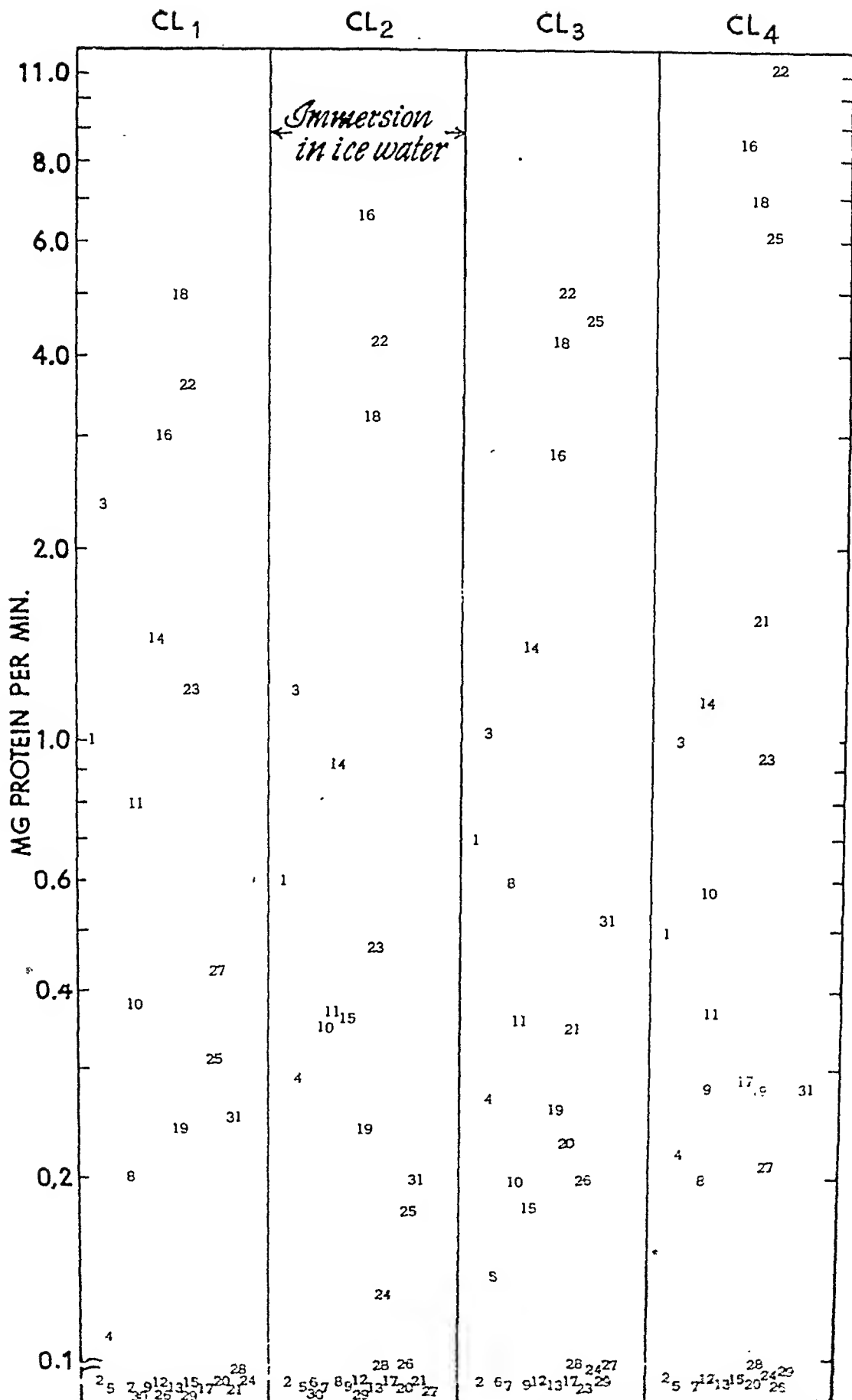


Fig. 5.—Renal response to thermal stimulus. Effect of ice immersion on protein excretion. Protein excretion expressed as mg. protein per minute on semi-log scale. CL-1 to 4 = consecutive clearance periods.

instances. In neither did immersion of one foot for fifteen minutes in an ice-water bath result in a decreased urine excretion. A third patient, however, in labor, was given a high spinal anesthesia to the level of thoracic 6. And immersion of one hand resulted in a reduced urine excretion (Table II).

Therefore, evidence obtained under anesthesia would suggest a sensory-humoral sequence, present during inhalation anesthesia, not secreted locally at the site of immersion, independent of the blood pressure response; probably stimulating a subcortical center, possibly the hypothalamus and pituitary gland, the latter liberating an antidiuretic hormone.

6. *Effect of Labor.*—It seems reasonable that the decrease in urine flow occurring during labor may be due in part to pain and apprehension. Verney¹¹ demonstrated a lag between absorption and excretion of lavaged water in dogs, a phenomenon attributed to the antidiuretic action of the posterior pituitary gland, which must be overcome before diuresis occurs. Employing this principle, patients were given 1,000 ml. 5 per cent glucose intravenously over a twenty-minute period before labor, and during early labor without sedation. The results (Fig. 7) indicate that the maximum diuresis occurs within thirty minutes in the former group, and the total urine flow usually exceeds 1,000 ml. within one and one-half hours. In the second group, however, the period of maximum diuresis is often delayed, and the total urine flow is much less for a comparable period. The same test on seven pre-eclamptic patients not in labor showed a similar anti-diuresis.

Comment

According to accepted theories, changes in the volume excretion of urine depend upon either the filtration rate or rate of tubular reabsorption, or both. Among the several factors influencing the former are: variations in filtration surface and changes in intracapsular pressure, renal blood flow or plasma protein content; while tubular reabsorption depends upon the rate of urine flow through tubules as well as upon the antidiuretic effect of the posterior pituitary gland. Either mechanism would explain a suppressed excretion following ice immersion. Wolf¹² obtained variable figures for renal blood flow and glomerular filtration (using diodrast and inulin methods) following cold exposure, but observed a sharp depression of both functions and a depressed urine excretion after other painful stimuli. Verney,¹¹ however, using a thermistor on the denervated dog kidney, recorded only a transient fall in renal blood flow following an electrical stimulus to subcutaneous tissues. This same investigator attributed the antidiuresis after such stimulus to a posterior pituitary effect. Recently, Trueta et al.¹³ report that renal arterial blood can be diverted past the kidney cortex to the medulla by sciatic nerve stimulation in dogs. Roentgenograms of the kidneys, following intra-arterial injection of radio opaque material, confirm this shunt, since there is a nonvisualization of the ipsilateral renal cortex, while the contralateral organ and the medulla of the ipsilateral side can be easily outlined. Urine excretion from the stimulated kidney is reduced. Apparently, some subcortical plexuses of vessels acts as the shunting route. Which of these three mechanisms might explain the urine suppression following ice immersion is largely problematical.

During normal pregnancy the kidney rarely concentrates chlorides well, the average being 0.5 Gm. per cent.¹⁴ During toxemic pregnancy this value

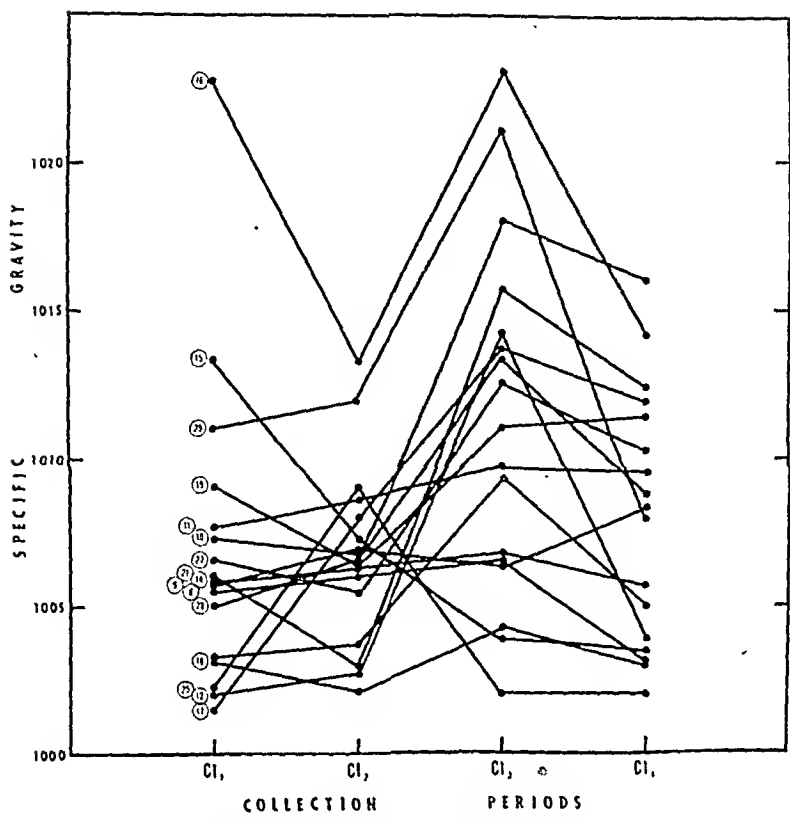


Fig. 6.—Renal response to thermal stimulus. Effect of ice immersion on urine specific gravity. Cl-1 to 4 = Consecutive clearance periods. Immersion during Cl-2.

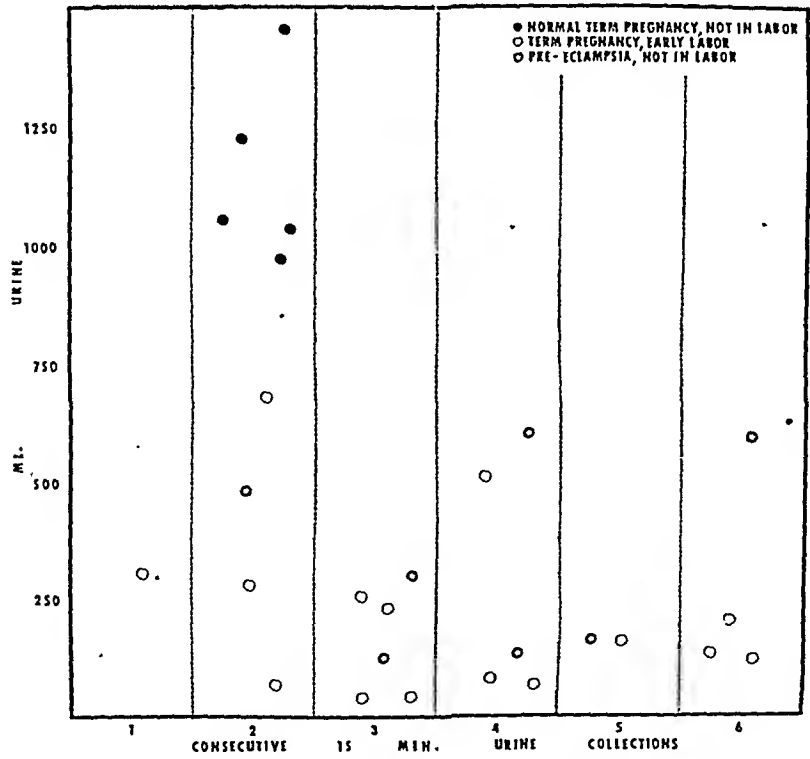


Fig. 7.—Renal response to thermal stimulus. Response to intravenous fluids. 1,000 ml. 5 per cent glucose commenced intravenously fifteen minutes previous to first urine collection and completed within twenty minutes.

Summary

The immersion of one hand, or foot, in an ice-water bath maintained at a temperature of 1° C. results in a decreased urine flow.

This phenomenon is associated with an increase in the specific gravity of urine, and in some instances, a change in protein excretion per minute.

Variations in systolic and diastolic blood pressure accompany this experience but do not correlate, in the degree of the response, with the protein excretion per minute.

The fetal heart rate does not vary significantly. Maternal pulse and respiratory rates tend to decrease.

Experiments to date conducted under anesthesia indicate that ice immersion may stimulate the liberation of an antidiuretic hormone. The site of liberation is probably not within the immersed limb, or within the kidney. Evidence presented supports its origin as being above the level of cervical 4. The phenomenon is apparently not abolished by inhalation anesthesia. It is believed that the site of liberation may be the posterior pituitary gland.

The authors are indebted to Dr. Wm. J. Dieckmann for advice concerning this study.

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5841 MARYLAND AVENUE

Discussion

DR. ARTHUR K. KOFF.—The secretion of urine by the normal kidney is dependent on a number of variable factors. (1) The renal blood flow, which is dependent on blood pressure, and the calibre (diameters) of the afferent and efferent arterioles of the glomerulus. A narrowing (constriction) of the afferent arteriole results in a decreased blood flow to the glomerular tufts, which in turn results in decreased secretion of urine. (2) The amount of urine secreted through the glomerular capsule depends on the filtration pressure which is determined by the difference between intraglomerular pressure, the resistance of the capsular membrane and the oncotic or osmotic pressure, particularly the blood proteins. It is estimated that 180 liters of urine are secreted through the glomerular capsule daily. Of this amount 177 liters of water and threshold substances are reabsorbed by the proximal and distal convoluted tubules and particularly in the loop of Henle. Chlorides are said to be absorbed in

is even lower, 0.185 Gm. per cent in 26 eclamptics. In patients with oliguria following eclampsia or abruptio placenta, we often observe a low urine specific gravity. Although these specimens appear to be concentrated, and contain considerable protein, the chloride content and corrected specific gravities are often low.

The fact that urine excretion was suppressed in some cases (Table II) without an appreciable rise in blood pressure, and the observation that the maximum reduction in urine flow occurred following (instead of during) changes in blood pressure, causes one to speculate that the two phenomena may be coincidental. Wolff and Hardy¹⁰ showed that the hypertension following ice immersion is a measure of the subject's reaction to cold pain. They also detected a local vasospasm during the experience and noted an increased cold pain if vasoconstrictor drugs, i.e., solution of posterior pituitary or epinephrine, were administered during immersion. It was, however, concluded that ischemia from spasm did not cause the pain.

Lipschitz and Stokey¹⁵ have observed that the mechanism of antidiuresis is not a single one. They postulate (1) an acetylcholine-antidiuretic hormone mechanism, arising from stimulation of the posterior pituitary gland, (2) one associated with renal innervation, being absent in animals with denervated kidneys subjected to injections of morphine, and (3) a humoral factor different from the antidiuretic hormone. Of these, the first, that involving the posterior pituitary gland, would seem to explain the antidiuretic effect of ice immersion.

On the other hand, it is difficult to explain the antidiuresis following ice immersion as being entirely due to a posterior pituitary stimulation since a decreased renal blood flow and glomerular filtration rate have been observed following painful stimuli,¹² and even following exposure to the cold test.¹⁶

Smith,¹⁷ in a recent review, traces the neural pathways controlling the pituitary gland. The mammalian hypophysis consists of neural and glandular portions. The posterior lobe comprises the neural portion and the pars intermedia of the glandular portion. It is in the pars nervosa that the antidiuretic hormone is elaborated. And this tissue receives nerve fibers from several hypothalamic nuclei, but chiefly from the bilateral supraoptic nuclei. These tracts become destroyed in diabetes insipidus. It is of interest that one patient in this experiment had diabetes insipidus, yet exhibited a suppression of urine flow following ice immersion.

Brun et al.¹⁸ studied kidney function during the transient circulatory collapse produced by a prolonged upright position on a tilt table, and found the inulin and diodrast clearances reduced during and following this experience. It was concluded that the reduced urine flow from the collapse was due to an increased secretion of an antidiuretic hormone. Drury et al.¹⁹ made similar observations following the continuous pressure breathing of oxygen. Bradley and Bradley²⁰ found kidney function suppressed during increased intra-abdominal pressure. It would seem that the same mechanism was responsible for the decreased urine flow following syncope, pressure breathing, and increased intra-abdominal pressure; and possibly following immersion in ice water.

ELDERLY PRIMIPARAS*

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THIS is a study of elderly primiparas, 35 years of age and over, taken from the records of St. Luke's and Cook County Hospitals in Chicago, Ill. It was necessary to review a larger number of years at Cook County to collect the same number of cases as at St. Luke's. The cases from Cook County are those of a purely charity service and those from St. Luke's are predominantly private cases of a closed staff. The patients considered are all individuals who were pregnant 7 months or more and who had viable babies on admission to the hospital. The oldest primipara at St. Luke's was 48 years of age and the oldest at Cook County was 45 years of age. A study of Table I shows that the patients at Cook County were predominantly Negro, while those at St. Luke's were predominantly white. It is noted that the percentage of elderly primiparas was five times as much at St. Luke's as in the Cook County patients. The number of patients in each age group was approximately equal for both hospitals as were the types of presentation. The incidence of breech presentation in each series was almost 6 per cent, as compared to 3 per cent in patients of all ages. Usually a higher incidence of twins is noted in elderly primiparas but there was only one set in 417 cases. Shoulder presentations are also supposed to occur more frequently in elderly primiparas but there was only one in the entire group.

The maternal mortality rate for all patients at both hospitals is very much the same, as may be seen in Table II. However, the maternal mortality rate of elderly primiparas in the private patients was more than twice the general mortality rate, whereas there were no deaths in the Cook County series. We still feel that a higher mortality can be expected in these elderly primiparas, due to age and accompanying degenerative diseases and the increased frequency of cesarean section. In most of the reports on elderly primiparas, maternal deaths occurred most frequently following cesarean section. Therefore, we feel that cesarean section should be carefully considered before being done and every effort made to deliver these patients from below. The one death in this series followed as an immediate operative complication of cesarean section. The section was done on a 37-year-old primigravida after a twenty-hour labor of poor quality with indifferent contractions, 9 cm. dilatation, ruptured membranes of three and one-half hours' duration, and the head not impressible below the spines. A normal male child was delivered. The uterus failed to contract under massage, Ergotrate and Pituitrin, and it continued to remain flabby and a considerable amount of bleeding ensued. A hysterectomy was decided upon because of the impossibility of controlling bleeding. As the clamps

*Presented before the Chicago Gynecological Society, Oct. 17, 1947.

the distal convoluted tubule. The antidiuretic hormone is responsible for 20 per cent of the water reabsorbed. The lack of this hormone is responsible for the marked diuresis in diabetes insipidus, and conversely an increase in the antidiuretic hormone could cause a more rapid reabsorption of urine from the tubules resulting in a marked decrease in urine output.

Dr. Odell has shown that under the influence of a standard pain stimulus (immersion of the hand in cold water) there is an initial rise in blood pressure due to generalized vasospasm. Apparently spasm of the arterioles to the glomeruli produces a decreased renal blood flow, and consequent decrease in urine excretion. However, the blood pressure returns to normal in five to eight minutes, but the decrease in urine output during the following fifteen minutes is even greater than the previous period of the test. This phenomenon he suggests may be due to the stimulation of the neuro hypophysis through the hypothalamus, and the release of antidiuretic hormone. The increase in this hormone causes increased reabsorption of water by the kidney tubules, and a consequent decrease in excretion of urine.

Dr. Odell's contention is supported by the work of Dieckmann and Michel who showed similar urinary excretion curves after the injection of posterior pituitary extract.

Verney, in 1946, by injecting hypertonic salt solution into the carotid artery of dogs, showed a similar urinary excretion curve which was abolished by hypophysectomy. Moreover, his experiments suggest that the blood chlorides to a great extent control the release of antidiuretic hormone by the posterior pituitary.

It is possible, therefore, that the oliguria and occasional anuria recognized in severe pregnancy toxemias may be due to the effect of the antidiuretic hormone rather than to the vascular spasm associated with the increased blood pressure.

As a matter of fact Putnam and Teel, many years ago, demonstrated antidiuretic substances in the urine of pregnant women with severe toxemia.

DR. WM. J. DIECKMANN.—This report by Dr. Odell forms part of the study he is making on blood pressure and renal function.

The obstetrician sees more cases of oliguria and anuria than almost any other specialist, with the exception of the urologist. This work demonstrating the close connection in some patients between external stimuli and urine output indicates the possibility of a combination of conditions under which the pregnant patient can be placed that might result in oliguria. A decrease in the urine output is found in eclampsia, in certain patients with hypertension, with hypotension from shock, and also in cases with peritonitis. A simple deprivation of water within a couple of hours in a very hot, dry atmosphere, may result in anuria.

The work also demonstrates that the kidney is not an isolated organ. Ten years ago we talked about "kidney disease," "liver disease," etc., but now we know that these various organs do not act as units but are dependent upon each other and the condition of the body as a whole.

DR. ODELL (Closing).—Our interest in this problem relates to studies on the oliguria and anuria in patients with toxemia of pregnancy. One should recognize that the kidney will respond to various sorts of external and internal stimuli by a reduction in urine flow. Although such changes may not be of importance to the normal individual, they may become irreversible in the pathologic state, particularly in those conditions in which the vascular system is already disturbed.

The relief of pain in toxemic patients becomes a real problem. The usual drugs employed (such as morphine and sodium Amytal) pharmacologically have an antidiuretic effect. We have administered sodium Amytal intravenously to toxemic patients and noted this antidiuretic effect is independent of changes in the glomerular filtration rate (mannitol) and renal blood flow (para-amino hippuric acid).

higher than in the private series. This may be explained by the higher rate of cesarean section at St. Luke's, the slightly lower incidence of toxemia and syphilis, and the fact that all patients had adequate prenatal care. In reviewing the fetal deaths in this series, it would seem that severe pre-eclampsia caused quite an increase at Cook County. A résumé of the fetal deaths follows:

St. Luke's Hospital

1. A severe pre-eclamptic at term entered the hospital in false labor. Patient was treated conservatively and blood pressure dropped. Six days after admission, patient went into labor spontaneously and after twelve hours of labor the fetal heart tones disappeared. Twenty-four hours later she delivered a 3-pound stillborn infant.

2. Patient febrile on admission to the hospital, fetal heart tones 180, patient in poor or questionable labor. Vaginal examination early in labor revealed wide separation of sutures of baby's head and it was questionable as to whether this was a baby in good condition. Vaginal delivery was decided on. After 128 hours of labor, baby was delivered by midforceps after Dührssen's incisions. Baby died in twelve hours and autopsy revealed tentorial tear.

Cook County Hospital

1. Pre-eclamptic of eight months' gestation, with blood pressure of 170/95 and 3+ albumin. Patient was treated conservatively for twelve days and went into spontaneous labor. Heart tones were lost after four hours of an eight and one-half hour labor. Autopsy revealed subaponeurotic hematoma.

2. Pre-eclamptic at term who had had no prenatal care. Entered the hospital in labor with blood pressure 190/120 and a 3+ albumin. Heart tones disappeared just before patient delivered after a nine hour labor. Autopsy revealed a congenital atelectasis, intrameningeal hemorrhages, and hemorrhage into the orbits.

3. Thirty-nine-year-old mild pre-eclamptic one month from term with partial abruptio. Baby delivered after a three hour labor, gasped a few times and could not be revived.

4. Seven months' gestation in a 39-year-old woman under treatment for syphilis. After a four and one-half hour labor, a 2-pound, 2-ounce baby delivered by breech. Baby died in twenty-four hours.

5. Forty-year-old pre-eclamptic of seven months' gestation with a blood pressure of 165/110, 2+ albumin, and thrombophlebitis. After a twenty-nine hour labor, patient spontaneously delivered a 3-pound baby who lived three hours. Autopsy revealed massive intraventricular hemorrhage of the brain.

6. Forty-year-old pre-eclamptic of eight months' gestation with a blood pressure of 180/126, 2+ albumin, and in labor with ruptured membranes. Baby delivered by breech after fifteen and one-half hours' labor and died four days alter. Autopsy revealed atelectasis and petechial hemorrhages of pleura, pericardium, and peritoneum.

7. Thirty-eight-year-old pre-eclamptic with blood pressure 168/92, 2+ albumin, and in labor. After twenty-one hours of labor, head was delivered by low forceps but shoulders were caught by constriction ring. This relaxed after thirty minutes and baby was delivered dead.

8. Thirty-eight-year-old diabetic with temperature of 102° F. entered ward and immediately delivered baby by breech. Baby died after several hours and autopsy revealed intracranial hemorrhage.

The more common complications of pregnancy as well as labor are shown in Table IV. With the increase in the age of the patient, there is an increase in the degenerative diseases, particularly of the cardiovascular and nephritic systems. There was a high incidence of pre-eclampsia and hypertensive toxemia. Fibroids were also a common complication in these older women. Prolonged labor was one of the most common complications. There was a much higher incidence of postpartum hemorrhage in the private series, but we feel this is due to the increase in the percentage of operative deliveries, necessitating deeper anesthesia. The high incidence of abruptio is expected to run parallel to an

were being applied to the broad ligament, the patient ceased to breathe. Resuscitation by stimulants and artificial respiration were useless. Autopsy revealed acute pulmonary atelectasis.

TABLE I

| ST. LUKE'S, JAN. 1, 1939, TO JULY 1, 1947 | TOTAL | PER CENT |
|---|--------|----------|
| All cases delivered, 7 months and over | 10,447 | |
| Elderly primiparas delivered, 7 months and over | 214 | 2.05 |
| Primiparas, aged 35 to 39 inclusive | 181 | 84.6 |
| White | 152 | |
| Negro | 29 | |
| Primiparas aged 40 and over | 33 | 15.4 |
| White | 28 | |
| Negro | 5 | |
| Vertex presentations | 202 | 94.4 |
| Breech presentations | 12 | 5.6 |
| COOK COUNTY, JAN. 1, 1937, TO JULY 1, 1947 | TOTAL | PER CENT |
| All cases delivered, 7 months and over | 50,677 | |
| Elderly primiparas delivered, 7 months and over | 203 | 0.4 |
| Primiparas aged 35 to 39 inclusive | 172 | 84.7 |
| White | 54 | |
| Negro | 118 | |
| Primiparas aged 40 and over | 31 | 15.3 |
| White | 11 | |
| Negro | 20 | |
| Vertex presentations | 189 | 93.1 |
| Breech presentations | 12 | 5.9 |
| Transverse presentation | 1 | 0.5 |
| Multiple pregnancy | 1 | 0.5 |

TABLE II. MATERNAL MORTALITY

| | | |
|---------------------------------------|------------|----------|
| St. Luke's total cases | 10,447 | |
| St. Luke's total case deaths | 21 or 0.2 | per cent |
| Cook County total cases | 50,677 | |
| Cook County total case deaths | 80 or 0.15 | per cent |
| St. Luke's elderly primiparas | 214 | |
| St. Luke's elderly primiparas deaths | 1 or 0.46 | per cent |
| Cook County elderly primiparas | 203 | |
| Cook County elderly primiparas deaths | 0 or 0.0 | per cent |

The fetal mortality rate was corrected to exclude all deaths except those due to an obstetric cause. Those babies dead on admission were excluded. Table III shows that the fetal mortality rates of all cases at St. Luke's and Cook County ran closely parallel, with a slightly higher rate in the Cook County series. This might be explained by the fact that many of these patients had no prenatal care. Along with this neglect of prenatal care, there was a higher incidence at Cook County of pre-eclampsia with its accompanying higher fetal mortality. The fetal mortality in the elderly primiparous series at Cook County was much

TABLE III. FETAL MORTALITY (CORRECTED)

| | TOTAL | DEATHS | PER CENT |
|-----------------------------|--------|--------|----------|
| <i>All Cases.—</i> | | | |
| Cook County | 50,677 | 1,035 | 2.04 |
| St. Luke's | 10,447 | 140 | 1.3 |
| <i>Elderly Primiparas.—</i> | | | |
| Cook County | 203 | 8 | 3.94 |
| St. Luke's | 214 | 2 | 0.93 |

indications in the vast majority of cases were purely obstetric and only after an adequate trial of labor. The abdominal pregnancy delivered a living baby which is now 3 years old, healthy, and normal. Cephalopelvic disproportion and pre-eclampsia were the main reasons for low cervical cesarean sections, while fibroid uteri were the predominating cause for Porro section. It is well to remember that the only death in this series followed as an immediate operative complication of cesarean section. The high incidence of cesarean section may be justified also by the fact that these are important babies to an elderly mother and this broadens our indications. However, we feel that in view of the fact that approximately 80 per cent of these elderly patients will deliver vaginally and that almost 75 per cent of the vaginal deliveries were short or average labors, an adequate trial of labor is indicated before cesarean is resorted to.

TABLE VI. DURATION OF LABOR (EXCLUDING CESAREAN SECTION)

| | ST. LUKE'S | | COOK COUNTY | |
|-----------------------------------|------------|----------|-------------|----------|
| | NO. | PER CENT | NO. | PER CENT |
| <i>35 to 39 Years of Age.—</i> | | | | |
| Short | 35 | 23.6 | 60 | 42.5 |
| 0-10 hours | | | | |
| Average | 72 | 48.6 | 62 | 42.5 |
| 10-24 hours | | | | |
| Prolonged | 41 | 27.7 | 19 | 13.4 |
| 24-hours and over | | | | |
| <i>40 Years of Age and Over.—</i> | | | | |
| Short | 4 | 22.2 | 6 | 25.0 |
| Average | 9 | 50.0 | 14 | 58.3 |
| Prolonged | 5 | 27.7 | 4 | 16.6 |

TABLE VII. CESAREAN SECTIONS

| | ST. LUKE'S | COOK COUNTY |
|---|------------|-------------|
| <i>Type.—</i> | | |
| Low cervical | 37 | 26 |
| Porro | 11 | 10 |
| Extraperitoneal | 0 | 1 |
| Abdominal pregnancy (living baby) | 0 | 1 |
| | 22.4% | 18.3% |
| <i>Indications (Low Cervical).—</i> | | |
| Cephalopelvic disproportion | 17 | 8 |
| Pre-eclampsia | 5 | 10 |
| Breech (with or without labor) | 4 | 0 |
| Uterine dysfunction | 3 | 7 |
| Fibroids (1 obstructing birth canal) | 3 | 0 |
| Elective | 2 | 0 |
| Double uterus, twins, previous myomectomy | 3 | 2 |
| placenta previa, transverse presentation | | |
| <i>Indications (Porro).—</i> | | |
| Fibroids | 9 | 7 |
| Elective | 1 | 0 |
| Hemorrhage following low cervical | 1 | 0 |
| Cervical dystocia with double mitral murmur | 0 | 1 |
| Previous myomectomy | 0 | |
| Abruptio placentae with Couvelaire uterus | 0 | 1 |

Summary

1. This is a study of elderly primiparas, 35 years of age and over, who were of approximately seven months' gestation and who entered the hospital with viable babies.

increase in the number of toxemia cases. It was of unusual interest that in two cases of pulmonary embolism complicating the puerperium, both followed a myomectomy done at cesarean section.

TABLE IV. COMMON COMPLICATIONS OF PREGNANCY, LABOR, AND PUERPERIUM IN ELDERLY PRIMIPARAS

| COMPLICATIONS | ST. LUKE'S | COOK COUNTY |
|-----------------------|------------|-------------|
| Pre-eclampsia | 23 | 27 |
| Fibroids | 10 | 11 |
| Hypertensive toxemia | 4 | 15 |
| Syphilis | 1 | 15 |
| Pyelonephritis | 2 | 1 |
| Diabetes | 1 | 2 |
| Abdominal pregnancy | 0 | 1 |
| Prolonged labor | 50 | 26 |
| Postpartum hemorrhage | 12 | 2 |
| Abruptio placentae | 5 | 4 |
| Placenta previa | 0 | 6 |
| Pulmonary emboli | 2 | 0 |

Table V shows the various types of vaginal deliveries. There were one-half as many spontaneous deliveries on the private service, twice as many low forceps, and twenty-one times as many midforceps. There were twice as many prolonged labors in the private series, which may explain the higher incidence of forceps deliveries. We think it is important again to emphasize the low incidence of postpartum hemorrhage in the Cook County series where the vaginal operative procedures were held down to a minimum. The high operative incidence had no marked effect on the fetal mortality in the private series where a low percentage of 0.9 per cent was obtained.

TABLE V. VAGINAL DELIVERIES

| TYPE | ST. LUKE'S | COOK COUNTY |
|-----------------------------|------------|-------------|
| Spontaneous | 55 | 113 |
| Low forceps | 83 | 42 |
| Midforceps | 21 | 0 |
| Spontaneous breech | 1 | 8 |
| Breech with forceps to head | 6 | 0 |
| Breech extraction | 0 | 2 |

The vaginal deliveries in these elderly primiparas were analyzed for type of labor. Short labor extended to a period of ten hours, average labor to twenty-four hours and prolonged labor to twenty-four hours and over. The shortest labors were approximately the same at both hospitals, in that they were about three hours' duration in the 35 to 39 year age group and approximately seven hours' duration in the 40 year age group. The longest labors in the 35 to 39 year age group were 128 hours at St. Luke's and 84 hours at Cook County. The longest labor in the 40 year and over age group was 42 hours at St. Luke's and 30 hours at Cook County. It can be seen from Table VI that, of the vaginal deliveries, approximately 75 per cent deliver with a short-to-average labor. Age after 35 is not too important a factor in the length of labor, as there appears to be no difference in the percentage in the various types of labor in the 35 to 39 age group and the 40 and over age group.

It is noted from Table VII that the incidence of cesarean section was 22.4 per cent in the St. Luke's series, as compared to a general average of 4.4 per cent for all patients delivered. The incidence of cesarean section at Cook County was 18.2 per cent where a general average of under 2 per cent exists. The

care if there is such a large number who do not now receive prenatal care on the voluntary basis? The third question which I would like to present is: Should we not use cesarean section more liberally in these elderly primiparas, rather than using it less? As surgery advances, the risk becomes less each year and it would seem that a fetal death rate four times as high in Cook County with fewer cesareans would mean that it should have been used oftener. Also, section should probably have been done in the only two cases of fetal death in the series at St. Luke's Hospital, rather than delivery from below, because one was a case of severe eclamptic toxemia and the other mother was allowed to be in labor 128 hours and then had her labor terminated by Dührssen's incision and midforceps. So far, in my twenty-four years of rather active practice I have not done any Dührssen's incisions.

I think the conclusion to be reached by this paper, as stated by the authors, is that 80 per cent of elderly primiparas will deliver their babies through the birth canal and 75 per cent of those will have an average-to-short duration of labor. I also think we are justified in drawing the conclusion that, when an obstetrician assumes the responsibility for an obstetric patient who has her first baby in the later years of her reproductive life, he assumes more responsibility than if the patient were at the age of 20 to 35 which seems to be the optimal time for a woman to reproduce.

DR. J. E. FITZGERALD.—I would like to answer a question or two of Dr. Galloway. Concerning prenatal care at the Cook County Hospital, one-third of the patients have prenatal care at the hospital clinic, one-third have prenatal care in other institutions, and one-third have no prenatal care. Dr. Galloway's question is well put, what should be done about it? As far as I am concerned, he can answer it.

I do not think it was the lack of pediatric care that was responsible for the deaths of eight babies in the Cook County series. Almost all of those were premature babies born to mothers with severe toxemias. Whether or not there were any pediatricians there, the salvage rate in babies born to mothers who have severe toxemia is much lower than where the mothers have no toxemia.

I am also quite certain that doing cesarean section on mothers who have babies that are markedly premature and who, themselves, have a severe toxemia will not result in any increase of the fetal salvage. Out of the entire series, only the patient who had a cesarean section died. Probably it is not too wise to increase the incidence of cesarean section in order to save premature babies of mothers who have severe toxemia, even though they happen to be over 35 years of age.

DR. GEITTMANN (Closing).—In this study we were primarily interested in learning whether these fetal deaths were due to obstetric causes, bad delivery, bad judgment in taking care of the patients while in labor or just before they went into labor, so we excluded those patients whose babies were dead on admission.

Answering Dr. Galloway's question, the woman who was in labor 128 hours was febrile when she came in. On admission the fetal heart rate was 180. It was felt that this was not a baby in good condition and that it would be better to deliver her from below, although cesarean section was considered.

2. Elderly primiparas occur five times more frequently in the private series than on a charity service.

3. Breech presentation occurred twice as often in elderly primiparas as in all cases.

4. Only one multiple pregnancy and one shoulder presentation occurred in 417 cases of elderly primiparas.

5. The maternal death rate was 0.46 per cent in elderly primiparas at St. Luke's as compared to 0.2 per cent in all cases; while at Cook County it was 0 per cent as compared to 0.15 per cent in all cases.

6. Corrected fetal mortality was 0.9 per cent and 3.94 per cent, respectively, at St. Luke's and Cook County hospitals, as compared to 1.3 per cent and 2.04 per cent in all cases.

7. Pre-eclampsia, hypertensive toxemia, and fibroids are the most common complications of pregnancy in elderly primiparas.

8. Prolonged labor occurred in 23.3 per cent of the elderly patients at St. Luke's and 12.8 per cent at Cook County.

9. Postpartum hemorrhage occurred more frequently in elderly primiparas at St. Luke's, where there was a higher operative incidence.

10. Approximately 80 per cent of the elderly primiparas will deliver vaginally and 75 per cent of these with short or average labors.

11. The cesarean section rate was 18.2 per cent at Cook County and 22.4 per cent at St. Luke's, as compared to 2 per cent and 4.4 per cent in all cases. Pre-eclampsia and cephalopelvic disproportion predominate as reasons for low cervical cesarean section, while fibroid uteri were the main reason for Porro section.

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Discussion

DR. CHARLES EDWIN GALLOWAY.—It is very interesting to note that 6 per cent of the cases were breech presentation, which is almost twice the usual incidence of breech. It is also interesting, but not surprising, to find that, in a private hospital, the primiparas over the age of 35 are about five times as numerous as in a large charitable service. The men at Cook County Hospital are to be congratulated on having no maternal deaths, but the fetal deaths were four times as great per 100 cases as in the private hospital. It would make one wonder if pediatrics at Cook County Hospital would be a factor in this high fetal death rate as well as obstetrics. The statement is also included that at Cook County Hospital there is no prenatal care. Also, the incidence of cesarean section for elderly primiparas at Cook County Hospital was considerably lower than at St. Luke's. It would seem, therefore, that prenatal care, more liberal use of cesarean section, and better pediatrics at Cook County Hospital would result in lower fetal mortality among the babies of elderly primiparas.

The only maternal death among the entire series was apparently due to hemorrhage. Today, the country over, hemorrhage has taken first place in the cause of maternal mortality. This is partly on a relative basis by having toxemia and infection reduced, but it is mainly because of our lack of adequate blood in the maternity wards and the fact that blood is not used as often and as soon as it should be.

One question which I would like to ask is: Why were the cases excluded when the patient was admitted with the baby dead in utero? The second question is: Why is there no prenatal care for patients delivering at the Cook County Hospital? Is there not something that can be done through the municipal government that might result in compulsory

The mothers of all the babies here studied represent a cross-section of the population which subsist on a somewhat better than average income. Private patients made up 36 per cent of the control group and 34 per cent of the vitamin B complex group. The remaining 64 per cent of ward-service cases in the control group and 66 per cent in the vitamin B complex group came from a better than average economic population than is ordinarily seen on the ward service. From this alone it is felt that the vitamin B complex status of these parturients is certainly no worse than any comparable sample of patients in this country.

Method

A total of 108 alternately unselected infants admitted to the neonatal nursery from the delivery room were given an aqueous extract* containing standard vitamin B complex factors. The remaining 138 infants were used as controls. The dose of extract administered was 0.12 c.c. (2 minims) of extract to 30 c.c. (ounce) of feeding. The average intake of human or cow's milk for each infant was 300 c.c. daily with a minimum of 210 c.c. and a maximum of 420 c.c. equally distributed in both groups. Over 75 per cent of the infants accepted approximately 300 c.c. of milk daily, and the approximate quantity of measurable vitamin B factors administered to each infant daily is shown in Table I. The exact quantity of each vitamin received daily was, of course, determined by the volume of milk fed to the infant. Those infants receiving artificial formulas had the extract added directly to the milk mixture. The breast-fed infants were offered a proportionate amount of extract in between-feeding water dependent in quantity upon the difference in ante-prandial and post-prandial weight. The vitamin factors were added to the 5 per cent beta-lactose or other solution used in the first two days of life preceding the onset of regular feedings in all babies. The only difference in the management of the *control* and *vitamin B complex* series was the addition of the vitamin factors in the latter. Premature infants of less than 2,500 Gm. birth weight, those over 4,500 Gm., and those with marked abnormalities (erythroblastosis fetalis 1, mongolian idiocy 2, spina bifida 1) were excluded from the series studied since the inclusion of these infants in the relatively small number studied might seriously have altered the statistical significance of our results. The number of infants thus eliminated from the series was approximately equal for both groups (nine from control group and seven from B complex group). The birth weight curves for both series followed one another and also the normal standard curve of distribution closely with no significant variation, ranging from 2,500 Gm. (1 per cent for controls and for B complex) to a peak at 3,500 Gm. (10 per cent for both series). All weights were determined under identical conditions by but two nurses at the same hour each day. Males made up 57 per cent of the control series and 63 per cent of the B complex fed infants. The type of feedings offered in both groups is shown in Table II and reveals no significant variation in either group.

*The quantity of the factors per c.c. of B complex administered can be found in the following table as computed by Parke-Davis and Co. and S. M. A. Co. from whom the material was obtained.

| | |
|--|-------------------|
| Thiamin | 0.25 mg. per c.c. |
| Riboflavin | 0.20 mg. per c.c. |
| Nicotinic acid | 1.25 mg. per c.c. |
| Pyridoxine | 0.10 mg. per c.c. |
| Pantothenic acid | 0.25 mg. per c.c. |
| Other undetermined fractions not measured. | |

VITAMIN B COMPLEX IN NEONATAL FEEDING

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(From the Obstetrical Department of the Henrotin Hospital)

THE oft-quoted statement of Oliver Wendell Holmes that "a pair of substantial mammary glands have the advantage over the two hemispheres of the most learned professor's brain in the art of compounding a nutritive fluid for infants" must be considered in a new light, since the importance of vitamins in the diet of infants has been elucidated. That human breast milk as well as cow's milk is deficient in vitamins A, C, and D has long been recognized, and the use of these factors to supplement infant feeding has had wide acceptance. The part played by the vitamin B complex of factors has unfortunately been widely disregarded, in spite of accumulating evidence that it too is inadequate in most instances. Hoobler, Outhouse, and Macy¹ demonstrated, for instance, that whereas 2.0 c.c. of human breast milk daily were adequate in vitamin A content to prevent xerophthalmia in rats, fully 20 to 25 c.c. of human milk were essential to offer sufficient vitamin B complex for approximately normal growth, reproduction, and lactation.

The value of the vitamin B complex in infant feeding has begun to receive recognition especially in the diet of the premature infant. Barnes and Willson² have advised the use of concentrated whole yeast extract in the diet of premature infants, and this tendency has been noted in many premature nurseries. It has, however, been more or less neglected as a supplemental factor in normal term infant feedings in spite of repeated expressions in the literature advising its more extensive use. With this in mind it was felt pertinent to evaluate the effect of vitamin B complex when added to the diet of normal newborn infants in the first ten days of life on the initial weight loss, the rate of return to the birth weight, and the weight at discharge. Osborne and Mendel³ demonstrated that the vitamin B requirements of rats increased rapidly with an increasing rate of growth, and it is obvious that growth in infants is most rapid in the first three months of life when the increment in weight is expressed as a per cent of the birth weight. Bloxson⁴ administered the mixed vitamin B to 34 young infants, as well as infants up to 2 years of age, and found that they gained an average of 100 per cent more in weight each day and remained in the hospital one-third less time. It is significant in his group of cases that a single premature received vitamin B complex from the second day of life, while the others were not placed on this supplement for two to three weeks after birth, and this premature infant gained relatively more rapidly than any of the others studied.

erature and widely variant practices adhered to in many newborn nurseries prompted this definitive study of the effect of a vitamin mixture of several factors of the B complex when added to the routine neonatal feedings.

The minimum daily requirement of the B complex vitamins have never been completely established for infants, but reports of Knott^{5, 6} suggested 0.25 mg./kg. of body weight or 0.4 mg. daily for thiamin chloride as the minimal daily requirement and this agrees well with the levels suggested by the Committee on Food and Nutrition.⁷ The average thiamin levels reported recently for various milks are as follows: pasteurized cow's milk 0.026 mg. per 100 c.c.; boiled pasteurized cow's milk 0.024 mg. per 100 c.c.; evaporated cow's milk reconstituted with equal parts of water 0.019 mg. per 100 c.c.; human breast milk 0.020 mg. per 100 c.c. Thiamin chloride, a heat labile substance, tends to be even further depressed below the minimal daily requirements by the general practice of heating cow's milk in the preparation of infant feeding formulas. Riboflavin has also been studied in regards to the minimal daily requirements in infancy. As early as 1879 Blyth⁹ reported the presence in cow's milk of a substance which he called "lactochrome" that is apparently identical with riboflavin. According to levels set by the Committee on Food and Nutrition⁷ the minimal daily requirement of riboflavin for infants under one year of age is established as 0.6 milligram. The riboflavin content of human milk has been reported as 0.16 mg. to 0.52 mg. per liter, and cow's milk, 1.0 mg. to 1.5 mg. per liter by Neuweiler¹⁰ who considered both sources as border line for the infant's needs. At these values an infant would require a minimum of 1,000 c.c. of breast milk daily for its riboflavin requirements. Sherman and Lanford¹¹ felt that milk is a dependable source of riboflavin for the infant, although Goodman and Gilman¹² state that but 20 per cent of the mother's intake of riboflavin is excreted in her milk. A possible case of ariboflavinosis in a premature infant has been reported by Stevenson.¹³ The minimal daily requirement of nicotinic acid for infants under 1 year of age has been set at 4.0 mg. daily by the Committee on Food and Nutrition.⁷ Standards for the other components of the B complex vitamins have not yet been adequately established for small infants.

Macy, Outhouse, Graham, and Long¹⁴ found that 20 to 25 c.c. of cow's milk daily were necessary for the support of normal growth, reproduction, and lactation in rats. They felt that impaired growth of young rats during the lactation period is due essentially to the deficiency in the quantity of vitamin B complex in the mother's food supply, since three to five times the normal quantity of vitamin B complex was essential for an adequate supply of these factors in the milk.¹⁵ They further stressed the fact that pooled human breast milk taken from individuals subsisting on an average American diet is deficient in vitamin B complex. Further, Cowgill¹⁶ demonstrated that subclinical vitamin B complex deficiency exists widely in the United States, as did Hoobler¹⁷ for infants.

Hess¹⁸ stated as an incidental finding in a study of the therapeutic value of yeast and wheat embryo in infantile scurvy that a definite increase in appetite and growth was noted in the yeast fed infants. Lactating rats were found by Sure¹⁹ to increase rapidly in weight when vitamin B complex was added to the

TABLE I. QUANTITY OF B COMPLEX FACTORS ADMINISTERED DAILY TO MORE THAN 75 PER CENT OF ALL TEST INFANTS

| | |
|------------------|----------|
| Thiamin | 0.30 mg. |
| Riboflavin | 0.24 mg. |
| Nicotinic acid | 1.50 mg. |
| Pyridoxine | 0.12 mg. |
| Pantothenic acid | 0.30 mg. |

TABLE II. TYPE OF FEEDING. CONTROL TOTAL—138, B COMPLEX TOTAL—108

| | BREAST | | ARTIFICIAL | | BREAST AND COMPLEMENT | |
|-----------|--------|----------|------------|----------|-----------------------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Control | 34 | 25 | 18 | 13 | 86 | 62 |
| B complex | 22 | 20 | 18 | 17 | 68 | 63 |

Results

From Fig. 1 it can be seen that the weight loss expressed as a per cent of the birth weight is approximately the same in both groups for three days after birth. This apparently demonstrates that there is no change in the physiological weight loss of the first three days of life which can be related to the presence of vitamin B complex in the diet. The weight gain which becomes apparent on the fourth day of life shows no significant early difference for either the control infants or those offered vitamin B complex. However, beginning on the seventh day and continuing until discharge on the tenth day of life there is a significant difference in weight gain for the two groups. The increase in weight gain for the B complex series is from 20 to 50 per cent greater than that for the control series in the last four days of the study.

The day on which the infants returned to birth weight in both control and B complex groups is shown in Fig. 2. Again it is clear that there is no significant difference between the return to birth weight of the control infants and those offered vitamin B complex until the seventh day of life. From that day to the day of discharge from the neonatal nursery the infants receiving added vitamin B complex in their diets returned to birth weight at a significantly higher rate. At discharge the cumulative difference in return to birth weight was more marked, with 80 per cent of those infants receiving vitamin B complex having returned or surpassed their birth weight, as compared to 59 per cent of the control infants who had regained their birth weight. Statistical analysis of this data for its probable significance reveals that, since all other things can be considered equal in both groups, the addition of vitamin B complex to the diet of the infants increased their chances of return to birth weight in the last four days of their stay in the neonatal nursery by 65 to 90 per cent.

When the significance of the return by 80 per cent of the B complex infants to birth weight on the tenth day of life is evaluated statistically as opposed to the control group of 59 per cent who returned to birth weight on this day, the results are very striking. The significance of these results are in the order of 1 in 2.4×10^{18} , a ridiculously small chance for error.

Discussion

The growing frenzy of vitamin therapy and prophylaxis which has swept the pharmaceutical industry and medical practice has also invaded the newborn nursery to an irregular degree. As is frequently the case, enthusiasm far outstrips clinical and laboratory knowledge in these matters. The voluminous lit-

diet. Dennett²⁰ gave 150 infants a diet rich in vitamin B complex, and found that the weight gain in five months was significantly greater than in controls without the wheat germ sugar mixture. He strongly advised the routine use of vitamin B complex in the diet of infants. Gaynor and Dennett²¹ added rice polishings as a source of vitamin B complex in the diet of 100 normal infants which had as controls 50 infants on the same rations without rice polishings and 20 infants on a simple cow's milk formula. The weight gain of those infants on the diet supplemented by rice polishings was uniformly greater than in either of the control series.

Although Elias and Turner²² reported no noticeable improvement in growth in 121 babies given brewer's yeast as a supplement to the diet over a long period of time, this evidence must be considered in the light of the excessively large quantities of brewer's yeast which are required for effective levels of B complex vitamins. Price,²³ on the other hand, reported that the addition of a vitamin B adsorbate to the diet of young infants resulted in a statistically significant increase in growth rate. A close relationship between vitamin B deficiency in the mother and premature labor was suggested by Clansen,²⁴ who also reported a definite augmentation of growth rate in premature infants offered supplementary vitamin B complex in their diet. Litchfield and his collaborators²⁵ and others have reported similar results.

The study here reported demonstrates sufficiently gross differences both in weight gain and in number of infants returning to birth weight within the first 10-day period of neonatal life. If there is any correlation between economic status and adequacy of diet in this country, both groups of patients can be considered as in a better than average state of nutrition. However, irrespective of the problem of variability and adequacy of the maternal diet, the fact that both groups of mothers were obtained without discrimination from identical sources suggests that there should be no significant difference in the antenatal vitamin levels of either the control or B complex groups. In order to eliminate variations which might be due to abnormal infants, those of excessive birth weight, prematures under 2,500 Gm., and infants in any way embarrassed during parturition by the usual obstetric factors were eliminated from either series at the time of admission to the nursery. This served but to clarify the premise that in the two groups of infants studied the only factor which separately identified a group was the presence or absence of the vitamin B complex. The parents, the birth weights, the method of choice of each group, the type of feeding, the sex, and the technique of handling the infants showed no significant variations. A compound containing many of the B vitamins was employed rather than specific members of this group, since the parts played in growth by the various factors in the B complex have not yet been clearly elucidated.

In view of the fact that the vitamin B complex content of both human milk and cow's milk are not considered adequate, the newborn infant may be considered to be in straitened circumstances as far as these factors are concerned. The fact that the response to vitamin B complex in weight gain is usually rapid enough to be noted in a few days suggested that a study of this effect in the first

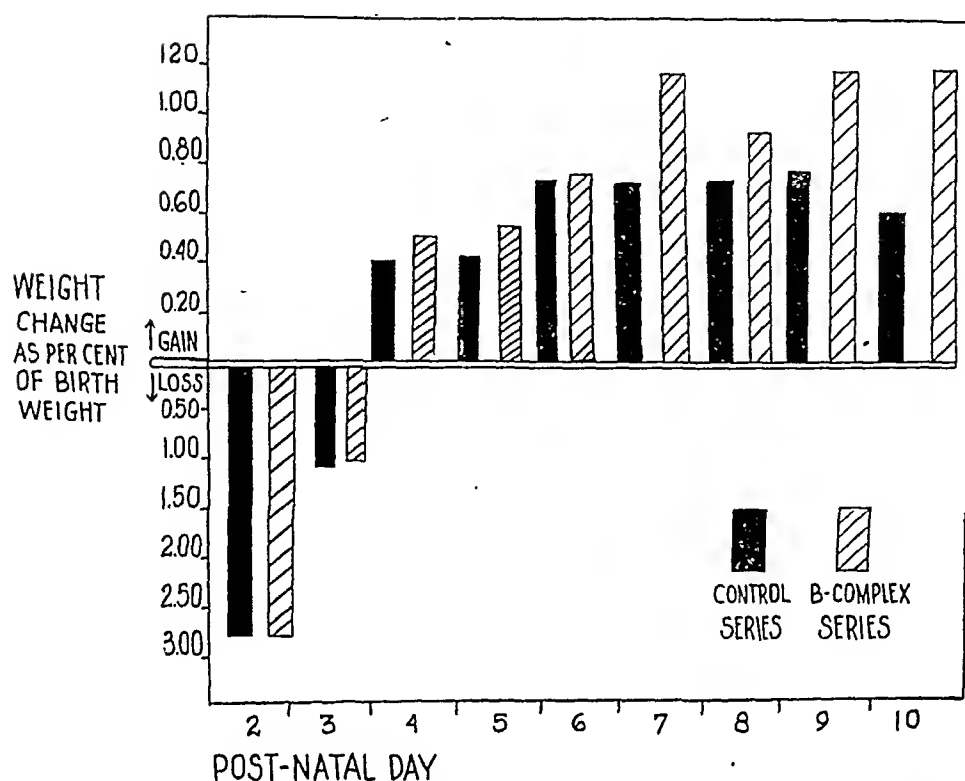


Fig. 1.—Average daily weight gain or loss as a per cent of birth weight.

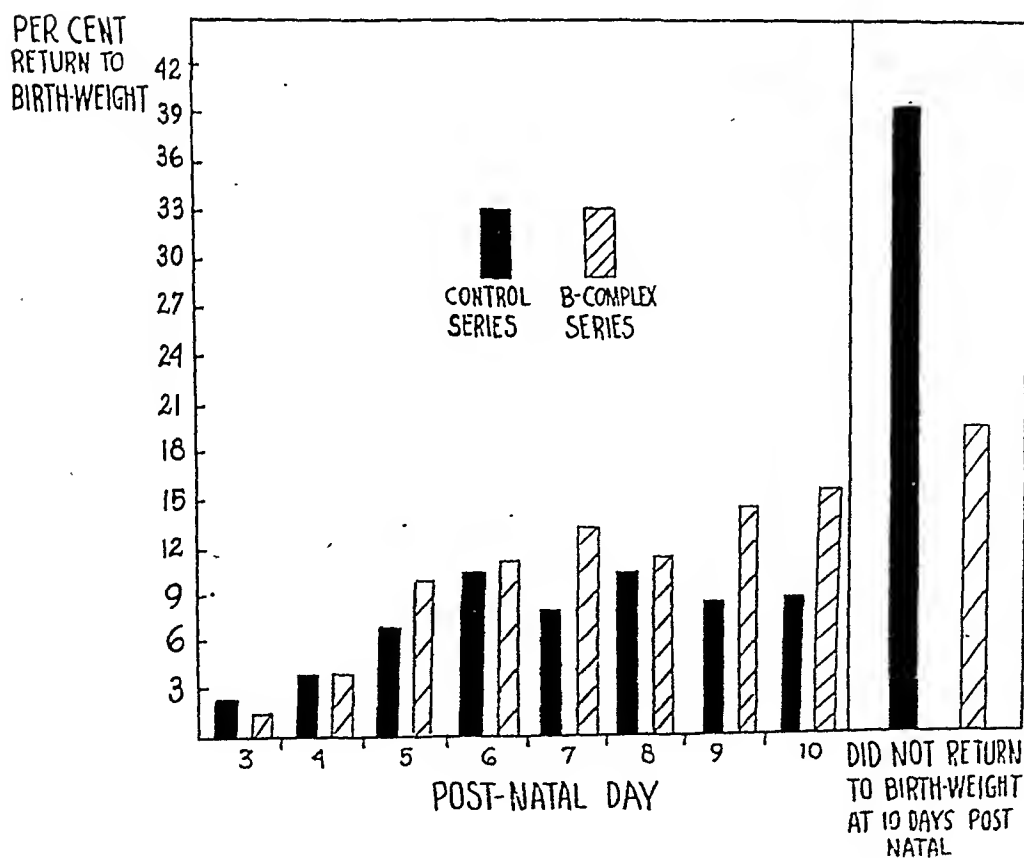


Fig. 2.—Day of return of infants' weight to birth weight.

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127 BAY STATE ROAD
122 SOUTH MICHIGAN BLVD.

ten days of life, that period usually spent in the obstetric nursery, was warranted. This is especially true since the weight gain is ordinarily very rapid in this period and the requirements of the infant for the essential factors present in the vitamin B complex especially great. It is felt that the material here presented demonstrates clearly that the addition of vitamin B complex to the diet of normal neonatal infants results in a significant increase in weight gain which becomes manifest at about seven days of life. This difference in weight gain is most notable when the number of infants returning to birth weight by the 10th day of life is compared in the two groups. It is therefore suggested that the diet of normal neonatal infants, as well as prematures, be supplemented by the addition of B complex vitamins to both breast-fed and artificially-fed infants from the onset of feeding.

Summary

1. Both cow and human milk are at the border line of the minimal daily requirements for infants with respect to thiamin and riboflavin content.

2. The usual practice of heating artificial cow's milk formulas employed in the feeding of infants further depresses the thiamin content of the milk.

3. Two closely comparable groups of infants were studied, the only significant difference being the addition of vitamin B complex to one group. The group of 108 infants given vitamin B complex during the first ten days of life showed an appreciable increase in weight gain during the last four days of the study as compared with 138 control infants. In addition, whereas 59 per cent of the controls had returned to birth weight by the tenth day of life, 80 per cent of the infants administered vitamin B complex had surpassed their birth weight by this day. Statistical analysis of the results reveals a ridiculously small chance for error in interpretation of the significance of the differences in weight gain and rate of return to birth weight in both groups studied.

4. It is suggested that vitamin B complex be added to the routine feedings of neonatal infants from the onset of feeding.

We would like to express our gratitude to Alan E. Rich, Longmeadow, Mass., for his statistical analysis of the data presented.

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TABLE I. VALUES FROM WHICH THE DATA OF FIGS. 2 AND 3 AND TABLE II HAVE BEEN DERIVED. THE AVERAGE CONCENTRATION OF D₂O IN THE MATERNAL PLASMA FOR THE DURATION OF THE EXPERIMENT HAS BEEN CALCULATED AS EXPLAINED IN THE TEXT. DELIVERY TIME REFERS TO THE INTERVAL BETWEEN I. V. INJECTION OF D₂O AND CLAMPING OF THE UMBILICAL CORD

| INDICATION FOR OPERATION | HISTORY NUMBER | GESTATION AGE WEEKS | DELIVERY TIME MINUTES | FETAL WEIGHT GM. | PLACENTAL WEIGHT GM. | TOTAL FETAL WATER C.C. | D ₂ O IN FETAL WATER | | D ₂ O IN MATERNAL BLOOD WATER | |
|--------------------------|----------------|---------------------|-----------------------|------------------|----------------------|------------------------|---------------------------------|----------|--|---------|
| | | | | | | | PER CENT | PER CENT | FOUND | AVERAGE |
| Chorea | 388120 | 14 | 9.0 | 58 | 92 | 53 | 0.180 | 0.330 | 0.330 | 0.617 |
| Psychiatric | 379368 | 16 | 10.5 | 113 | 44 | 100 | 0.172 | 0.240 | 0.240 | 0.449 |
| Cardiac disease | 376618 | 18 | 11.0 | 201 | 107 | 177 | 0.219 | 0.239 | 0.239 | 0.446 |
| Chronic pyelitis | 396381 | 31 | 10.8 | 1500 | 243 | 1215* | 0.183 | 0.260 | 0.260 | 0.486 |
| Previous section | 311276 | 33 | 11.5 | 2100 | 370 | 1637* | 0.142 | 0.174 | 0.174 | 0.325 |
| Previous section | 376433 | 37 | 13.0 | 3430 | 516 | 2439* | 0.085 | 0.180 | 0.180 | 0.337 |
| Contracted pelvis | 408367 | 40 | 9.3 | 2490 | 335 | 1857* | 0.054 | 0.220 | 0.220 | 0.411 |

*Values in viable fetuses have been calculated from the volume of distribution of D₂O, and the concentration of D₂O in water obtained by vacuum distillation from a sample of blood.

THE PERMEABILITY OF THE HUMAN PLACENTA TO WATER AND THE SUPPLY OF WATER TO THE HUMAN FETUS AS DETERMINED WITH DEUTERIUM OXIDE

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IN A previous paper,¹ findings were presented on the permeability of the human placenta to sodium as determined with the radioactive isotope and the theory of the tracer technique in investigations of this kind was discussed. Our present concern is with the permeability of the human placenta to water, using deuterium oxide (heavy water) as the tracer substance. As in other studies from this laboratory, we shall analyze our data from the viewpoint of the following questions: (1) Does the permeability of the human placenta to water change with the period of gestation? (2) Is the permeability of the human placenta to water approximately like that of another member of the hemochorial group, the guinea pig, as is true for sodium? (3) What is the relative permeability of the human placenta to water and to sodium? (4) Does the human fetus, like the fetus of the guinea pig, receive quantities of water greatly in excess of the amount incorporated in growth?

Method

Ninety-five per cent deuterium oxide (D_2O) made isotonic with sodium chloride was injected into seven patients whose pregnancies were being terminated by the abdominal route at various periods of gestation and for various reasons, as shown in Table I. Sufficient D_2O , from 40 to 70 c.c., was used to give an estimated blood concentration at equilibrium of about 0.2 per cent. Since it was desirable to administer this amount as quickly as possible, the injection was made simultaneously into both antecubital or both anterior tibial veins. Complete injection required about thirty seconds; the beginning of the period of transfer to the fetus was counted from the time when half of the D_2O had been injected. The fetus was delivered and the umbilical cord clamped after a known interval, approximately ten minutes later.

There is a tendency for D_2O which has reached the fetus to be lost by re-entering the maternal circulation. If there is equal freedom in the movement of tracer back and forth across the placenta, it can be shown mathematically² that this loss will increase as the concentration in the fetus approaches that in the maternal plasma. To calculate the loss is a rather complicated process. It is simpler to use the criterion applied in the studies with D_2O in guinea pigs²: as long as the quantity of tracer (compared with the concentration in the maternal plasma) increases linearly with time, error due to backflow is minimal. Accordingly the human experiments, on the basis of the experience with guinea pigs, were limited to a transfer period of ten minutes.

In order to establish the rate of disappearance of D_2O from the blood after intravenous injection, successive samples of blood were taken at intervals up to

difference between the weight of the fetuses before and after vacuum distillation to dryness. In the case of viable fetuses, this quantity was secured by measuring the volume of dilution of a known quantity of D_2O injected intravenously into newborn infants,⁵ and has the value of 74.6 per cent of body weight.

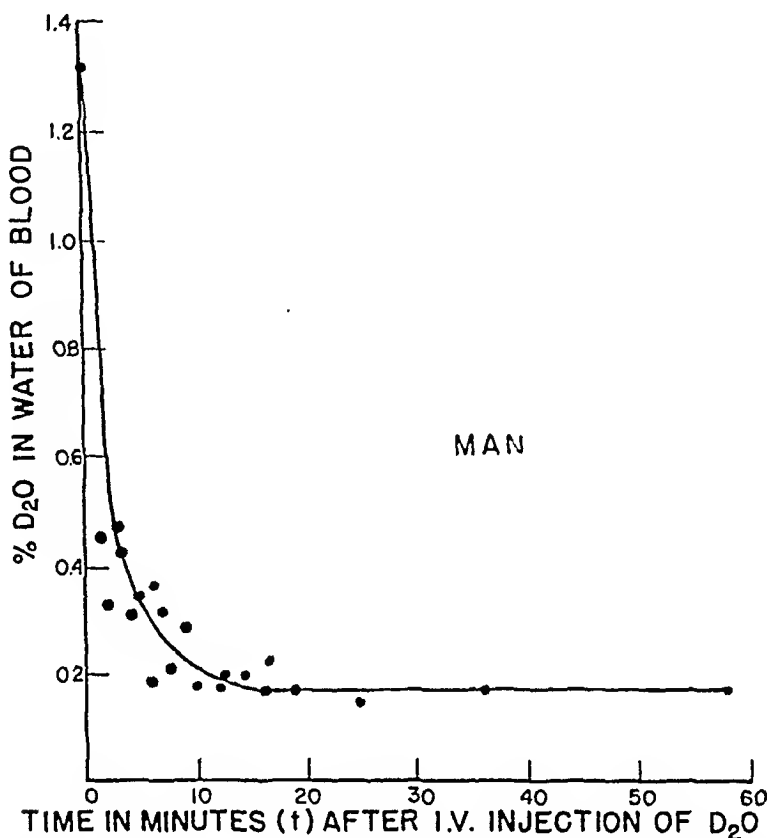


Fig. 1.—Change in concentration of D_2O in the water of the blood with respect to time. The measurements were made on three individuals, and observed concentrations of D_2O adjusted to an initial concentration of 1.3 per cent D_2O . To obtain the total water of the blood for calculation of the initial concentration of D_2O , we used the average volume per unit body weight of red cells in man as found by the radio iron technique,⁹ the average volume of plasma given by the dye method,⁹ and the water content of these two portions of the blood.¹⁰

The quantity of water transferred to the fetus per hour at various fetal ages is given in Fig. 2. It will be noted that the very large quantity of 3.6 liters of water per hour crossed the placenta to the fetus at the peak of the curve, which is at about the thirty-fifth week of gestation.

Using the values of Fig. 2 and Table I, the transfer of water per gram placenta per hour has been obtained by dividing the quantity of water transferred to the fetus in this time by the corresponding placental weight. These values are presented in Fig. 3. Although the cases are limited to seven, they describe a change in permeability entirely consistent with our rather large experience with sodium in man¹ and with several substances in animals.^{6, 7} In view of this and the costliness of the deuterium oxide, we feel justified in basing our conclusions on this series of seven. Closely approximating the results with sodium, there is about a fivefold increase in permeability from the fourteenth week of pregnancy, the earliest case in the series, to the peak which occurs at about the thirty-fifth week. This peak in permeability at the thirty-fifth week is followed by a sharp decline to term.

one hour after injection of D_2O in three pregnant subjects. A sample of blood was obtained from viable fetuses two and one-half to three hours after delivery. The placenta was freed from excess blood, membranes, and cord; then weighed. The water from the maternal and fetal blood or from the total fetuses (when nonviable) was obtained by vacuum distillation to dryness at room temperature, condensation being carried out in tubes surrounded by dry ice and alcohol. It is essential that the distillation be carried to complete dryness because of the difference in the rate of vaporization of H_2O and D_2O . The water was next purified by passing it over CuO in a combustion furnace and distilling it from alkaline permanganate and chromium trioxide as described by Keston, Rittenberg, and Schoenheimer.³

The concentration of D_2O in the samples was determined by a modification³ of the method of Barbour and Hamilton.⁴ This consists of measuring, at an accurately maintained temperature, the falling time of a drop of water of fixed volume through a column of immiscible fluid of slightly lower density. M-fluorotoluene at a temperature of $19.5^\circ C$. was used as the immiscible medium. Other details of the method including the micropipette were as described by Keston, Rittenberg, and Schoenheimer.³ Determinations on fetal water were run in duplicate, and checks to within plus or minus 0.01 per cent were obtained.

Results

The Disappearance Curve of D_2O From Blood After Its Intravenous Injection.—The calculation of the placental transfer rate for water depends upon an accurate estimation of the average concentration of D_2O in the maternal blood for the period of transfer under observation. The reasons for this, and the method of obtaining the average value, are essentially the same as those previously presented for sodium¹ and need not be repeated in detail here. A known quantity of D_2O was injected intravenously into each of three pregnant women. The experimentally determined observations on the three individuals were all adjusted to an initial concentration of D_2O in the blood water of 1.3 per cent which about equaled the concentration anticipated from dilution of the amount injected by the calculated blood volume of the subject (see legend of Fig. 1). Since D_2O in plasma comes very rapidly into equilibrium with the red blood cells, water of whole blood was analyzed for its D_2O content. The disappearance curve of D_2O from the blood is given in Fig. 1. It is evident that the concentration in the blood declines rapidly during the first ten minutes and that equilibrium between blood and extravascular fluid is not reached for about twenty minutes. The average value for the concentration of D_2O in blood during the first ten minutes of the experiment is 1.87 times the concentration observed at the end of ten minutes; consequently the content of D_2O in the maternal blood samples obtained ten minutes after beginning the experiment must be multiplied by the factor 1.87 to give the average concentration of D_2O during the period of transfer.

The Normal Placental Transfer Rate for Water at Different Gestational Ages.—As has been previously discussed,¹ the quantity of water transferred to the fetus during the course of an experiment can be directly calculated from three quantities: the observed concentration of D_2O in fetal water, the average concentration of D_2O in the water of maternal blood, and the total volume of water of the fetus, on the assumption that there is no separation of isotopes. If these quantities be designated respectively by D_2O_f , D_2O_{mb} and H_2O_f , then the quantity of water transferred to the fetus during the time of an experiment is equal to:

$$D_2O_f \times H_2O_f \div D_2O_{mb}$$

In the case of nonviable fetuses, total body water (H_2O_f) was obtained from the

Fetal Need for Water Relative to Its Supply Across the Placenta.—The ratio of the quantity of a substance supplied to the fetus from the maternal plasma to the amount of that substance retained by the fetus in its growth has been called the safety factor for that substance.¹ The quantity of water transferred per hour to the fetus across the placenta per hour is given in Fig. 2. The amount of water retained by the fetus in an hour's growth is equal to the fetal weight multiplied by the hourly per cent weight increase of the fetus multiplied by the total water in a unit weight of fetal tissue. The safety factor has been calculated for four fetal ages and is given in Table II. The value of the safety factor varies from 700 at a fetal age of fourteen weeks to the extraordinarily high value of 3,800 at thirty weeks. This means that of 3,800 parts of water delivered to the fetal circulation at thirty weeks, only one part is retained by the fetus in its growth and 3,799 parts are returned to the maternal circulation.

TABLE II. FETAL NEED FOR WATER RELATIVE TO WATER SUPPLIED ACROSS PLACENTA AT VARIOUS GESTATIONAL AGES. THE DAILY PER CENT WEIGHT INCREASE HAS BEEN CALCULATED FROM THE DATA OF STREETER¹¹

| GESTATION AGE WEEKS | FETAL WEIGHT GM. | DAILY WEIGHT INCREASE PER CENT | TOTAL WATER CONTENT OF FETUS C.C. | TOTAL WATER TRANSFERRED TO FETUS PER HOUR C.C. | TOTAL WATER RETAINED IN HOURLY GROWTH OF FETUS C.C. | SAFETY FACTOR |
|---------------------------|------------------------|---|---|--|---|------------------|
| 14 | 58 | 6.4 | 53 | 101 | 0.14 | 720 |
| 16 | 113 | 5.3 | 100 | 207 | 0.20 | 1100 |
| 18 | 201 | 3.9 | 177 | 406 | 0.29 | 1400 |
| 31 | 1500 | 1.3 | 1215 | 2500 | 0.66 | 3800 |
| 40 | 2490 | 1.1 | 1857 | 1580 | 0.85 | 2000 |

Discussion

The increase in the permeability of the placenta to sodium as gestation proceeds has been correlated with morphological changes in the placenta as it ages.¹ Variations in the permeability to water are similar to sodium and again it appears that thinning of the walls of the villi together with increase in area of placental exchange due to branching of the villi are fundamental factors underlying the increase in permeability. The terminal sharp decrease in placental permeability is probably due in considerable measure to the deposition of fibrin over the surface of the villus.

Striking correspondence has been observed in the permeability to sodium among four members of the hemochorial group¹: at the middle of the ninth tenth of gestation in man, 6.5 milligrams of sodium cross a gram of placenta per hour; in the guinea pig, 6.1 milligram; in the rabbit, 6.8 milligrams, and in the rat, 8.3 milligrams. Water transfer has been studied only in man and guinea pig; the difference in the permeability of their placentas to water is greater than could have been predicted on the basis of the results with sodium. Thus, at the middle of the ninth tenth of gestation about 10 c.c. of water cross a gram of the human placenta per hour, whereas about 20 c.c. of water cross a gram of the placenta of the guinea pig per hour. The meaning of this difference from the viewpoint of comparative physiology cannot be appraised without information on other members of the hemochorial group as well as representa-

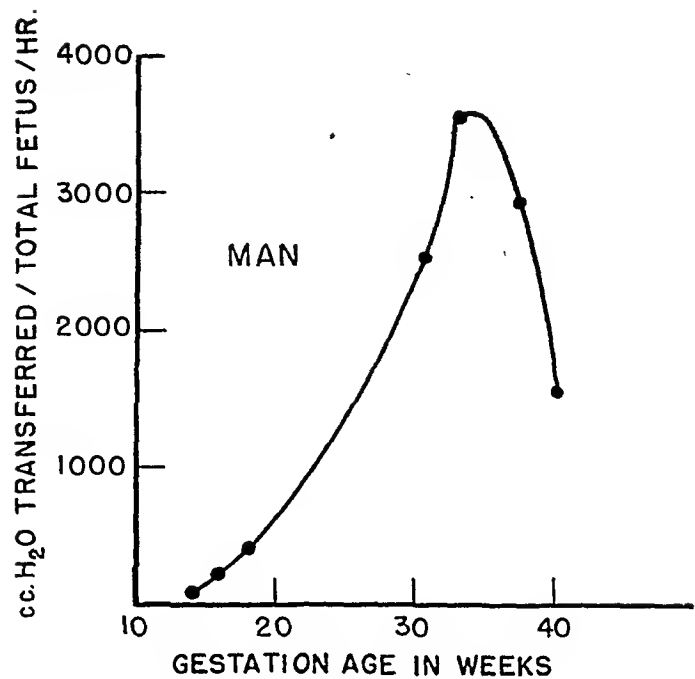


Fig. 2.—Variation of rate of transfer of water to human fetus with respect to gestational age.

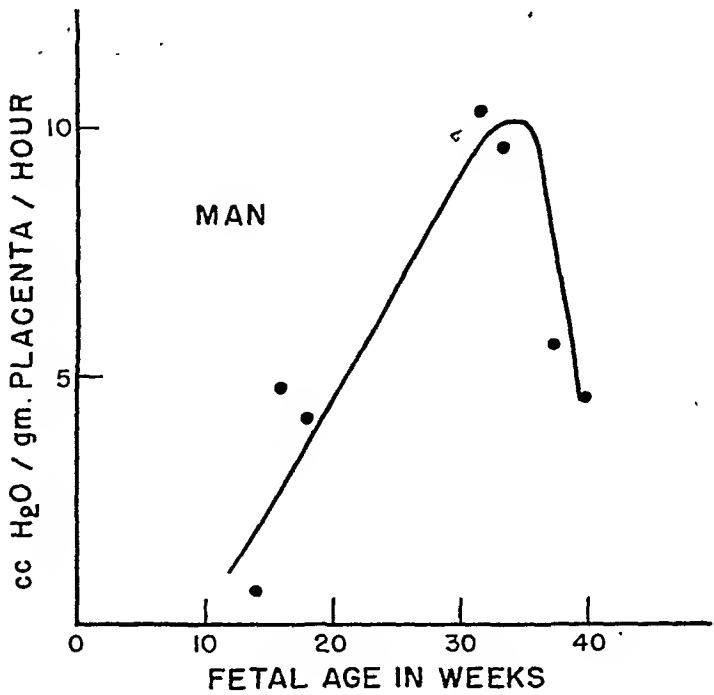


Fig. 3.—Variation of rate of transfer of water per unit weight of placenta with respect to gestational age.

of material across it and so acts as an inert membrane, it could properly be designated the permeability coefficient. Since the mechanism of transfer is unknown, it appears preferable to designate the coefficient as the transfer coefficient and so to avoid implication as to the precise nature of transfer.

The transfer coefficient for water and sodium as functions of gestational age are given in Fig. 4. The value for water is about five times that for sodium from the twelfth to the thirty-fifth week of gestation, i.e., the human placenta appears to be five times as permeable to water as to sodium. The difference in the behavior of water and sodium may be due to secretory activity by the membrane or to the physical characteristics of the membrane which permits water to pass through it more readily than sodium. Differences of this kind have been observed in a study of the relative rate of passage of water and sodium from the inside to the outside of a collodion sac.² No deductions, consequently, can be made about the nature of placental transfer from the difference in apparent permeability to sodium and to water.

Summary

1. Changes in permeability of the human placenta to water have been measured with deuterium oxide as the tracer material from the fourteenth week of pregnancy until term. There is about a fivefold increase in transfer rate of water per unit weight of placenta during this period.

2. The placental transfer coefficient for water is five times as great as that for sodium at corresponding periods of gestation.

3. The permeability of the placenta of the guinea pig to water has been found to be about twice that of the human placenta; this divergence is considerably greater than for sodium.

4. The human fetus receives across the placenta at the fourteenth week of gestation 700 times and at the thirty-first week 3,800 times as much water as is incorporated in the growing tissues.

The heavy water used in these experiments was kindly supplied by the Abbott Laboratories.

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tives of the other morphologic types of placenta. It serves as an example, however, of the uncertainty of making precise predictions about the behavior of one substance (in this instance water) from the behavior of another substance (in this instance sodium) among animals of the same or different types of placentas.

It is our purpose to characterize the placenta on the basis of its relative permeability to as many of the constituents of the maternal plasma as is possible. When this is accomplished, we shall be in a position to attempt to relate the physico-chemical properties of these substances to the rate at which they cross the membrane and to gain an insight into the forces which govern placental transfer. If the concentration of a normally occurring substance in the maternal plasma be designated as C_{mp} , the total quantity of this substance transferred to the fetus during the time, t , as Q_f and the weight of the placenta as W (W is taken to be proportional to the area of the transfer surface) then:

$$Q_f = kWC_{mp}t$$

in which the amount of substance transferred to the fetus in a certain time is assumed to be directly proportional to the concentration of the substance in the maternal plasma, to the weight of the given placenta, and to the length of the period of transfer. It is evident that the greater the apparent permeability of the placenta to a given substance, the larger will be the value of k .

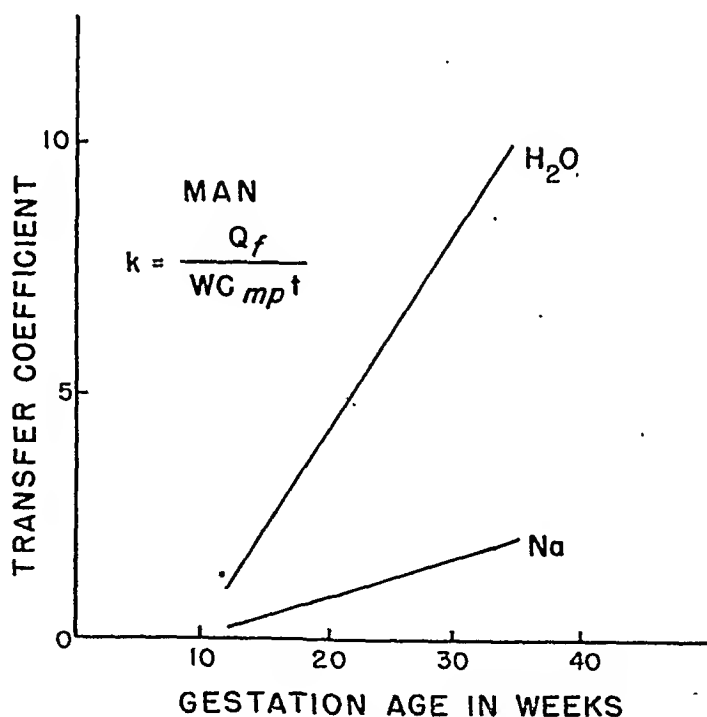


Fig. 4.—Placental transfer coefficient for water and sodium at various gestational ages. The coefficient is defined in the text.

The coefficient k is influenced by many factors. It probably depends upon the permeability of the placenta, i.e., the characteristics of the placenta as a membrane, the presence or absence of secretory activity by the placenta with respect to the substance and the physico-chemical characteristics of the substance. If it were certain that the placenta performs no secretory work in the transport

these cases occur in the absence of evident trauma and in spontaneous deliveries following easy labors. It has been observed that toxemia predisposes. This is possibly on the basis of vascular changes that accompany albuminuria and hypertension and that may account for retroplacental hematoma with abruptio placentae. Most cases occur in primiparas (59 per cent of the cases reviewed by Hamilton), but some of the most extensive damage has been seen in multiparas, as in our first and third cases. Another suggested factor is increased fragility of the vessels and hemorrhagic tendencies associated with constitutional diseases. In discussing Hamilton's paper in 1940, W. H. Rubovits told about a case of his that developed postpartum bleeding from the upper end of an episiotomy that was very difficult to control. After recovering from this, the patient died from hemorrhage at the back of the tongue that started from no more trauma than a passionate kiss. There are several cases reported that show bleeding at sites other than the pelvis, such as epistaxis and retinal hemorrhages.

There is a great deal of discrepancy of opinion as to the role played by varicosities of the veins in the perigenital region. In our first case, it is possible that they were a contributing factor. If a normal vessel can be accused of rupture, then we fail to see any defense for an already injured one. DeLee-Greenhill⁸ state that rupture of a varix in the broad ligament is one of the causes of obstetric shock.

Surgical repair of episiotomy or laceration may be a causative factor if a large vein or varicosity is pierced during the repair. Hematomas thus formed are seldom of consequence, as they are noted and tended to immediately or are small and resorb spontaneously. One reported case is ascribed to failure to secure hemostasis during the repair of the episiotomy.

Symptoms

The symptomatology is primarily pain and/or blood loss. Although the pain of tearing of the tissues during the formation of the hematoma is usually excruciating and forces the attendant to search out the cause, our third case developed the largest hematoma that we have seen and complained of pain only on motion. E. G. Lipow⁹ reports a case associated with rupture of perineal muscles with exacerbation of the pain at the time of rupture of each muscle. As large amounts of blood can be lost, the picture of anemia and shock is readily understandable.

Findings

The findings vary with the type of hematoma. Those that appear on the perineum or vulva are readily seen. Those limited to the vagina, however, have to be searched out with a speculum. Both appear as a tense, bluish, fluctuating mass that may have abraded or weeping surfaces. Those that occur above the cardinal ligaments have to be palpated bimanually or rectovaginally.

Differential Diagnosis

In the differential diagnosis, one must consider:

1. *Inversion of the Uterus*.—This can be ruled out by the absence of the uterus in the abdomen or pelvis, with notching at the attachment of the broad ligament, and manual definition of the tumor mass appearing in the vagina.

2. *Prolapse of the Cervix or Vagina*.—This can be definitely identified by careful inspection and the absence of pain and shock.

3. *Threatened Rupture of the Uterus or Rupture of the Uterus While the Baby Is Being Extracted*.—Bimanual and intrauterine examination will readily lead to a diagnosis.

PUERPERAL PERIGENITAL AND PERINEAL HEMATOMAS*

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PUERPERAL perigenital and perineal hematomas are accumulations of blood in the perigenital soft connective tissue resulting from the rupture of a blood vessel, usually a vein, ineumbent on the trauma of labor. Blood escaping into the soft connective tissue tends to follow the planes of cleavage of the fascia, and when this process occurs high in the genital tract, the blood tumor forms in or below the broad ligaments, in the perivesical space, or beneath the vesicouterine fold of peritoneum. These hematomas tend to dissect under the peritoneum and may extend upward under the inguinal ligament or posteriorly to the region of the kidney or the diaphragm. A hematoma occurring in the perivaginal region or the lower part of the birth canal forms a blood tumor that may close the vagina, distend the vulva and perineum, or displace the rectum or the urethra.

Such a complication usually occurs during the descent of the fetus or shortly after delivery. However, it has been reported by Frank-Kamenetsky¹ that a large hematoma, forming after the first twin, caused obstruction to the delivery of the second (in four cases), and that it is possible for a large tumor to form an obstruction to the delivery of the placenta.

DeLee-Greenhill² state that cases have been reported as late as twenty-one days post partum, and Lamm and Lamm³ recently reported a case occurring fourteen days post partum.

Incidence

The incidence of occurrence varies greatly. DeLee-Greenhill² state that they found an over-all incidence of one in 4,000 cases, but that large hematomas occurred only seven times in the pathologic work of 70,000 cases, or 1:10,000. Michaels and Herring,⁴ of New Orleans, report one in 5,474 cases, Williams⁵ reports one in 2,000 cases, while Moshkow⁶ has an incidence as low as one in 1,951 cases. One of the factors responsible for the discrepancy is, of course, the fact that frequently the tumors are small and insignificant or undiagnosed. In 1940, when Hugh Hamilton⁷ reviewed the literature, he was able to find only 156 cases, including twelve of his own. Since that time, eight new cases have been reported in the United States literature.

Etiology

The etiologic factor is primarily trauma resulting in the bursting of a blood vessel. In the delayed type, pressure necrosis is the injury that results in delayed blood loss. This cannot be the entire story, however, as too many of

*Presented before the 588th regular meeting of The Chicago Gynecological Society, Oct. 17, 1947.

of a small rupture immediately post partum, but the equivocal findings did not conform to the impression. However, the specimen in situ looked like a small rupture after the hematoma was removed from the uterus. Only after the uterus was removed was it determined that no rupture existed. The sections did show hemorrhage infiltrating the myometrium, which was so obviously damaged in the gross specimen.

The suggestion of the etiology of the hematoma is the other point of interest. The persistent bregma incarcerated the lower uterine segment and the bladder between it and the symphysis pubis and mashed this tissue under the pressure of the uterine contractions. This is similar to the mechanism of a colporrhexis when the occiput is directed against the sacral promontory as in a case of pendulous abdomen.

We believe the management of this case terminated the pathologic mechanism while the damage was only a hematoma and threatening rupture of the uterus. We believe the failure to interfere would have led first to an incomplete and then to a complete rupture of the uterus. The forces which ruptured the vessels and led to the hematoma are the same that, if prolonged, can rupture the uterus.

CASE 2.—Mrs. M. T., a 36-year-old, white primipara, was admitted to the hospital on June 15, 1947, in active labor. She had had adequate prenatal care. Although every attempt was made to limit this patient's diet, she persisted in overeating and gained 46 pounds. In the last three weeks of her prenatal period, she developed a low-grade toxemia, with a blood pressure at times up to 140/100 and albuminuria of from 20 to 50 mg. There was a moderate degree of water retention and edema of the feet and legs. She was admitted to the hospital eight days before her expected date of confinement and was found to have a blood pressure of 140/100. The position was right sacrum anterior. The fetal heart tones were 140, and she was in active labor, with pains occurring every four minutes, of moderate intensity and lasting thirty seconds.

She was given sedation, and labor progressed rapidly. In three and one-half hours, she delivered with manual aid and a left mediolateral episiotomy a six pound, five ounce female infant.

During the repair of the episiotomy a hematoma about 4 cm. in diameter was noted in the left vaginal wall, about 3 cm. above the top of the incision. During a period of observation, the hematoma was seen to be self-limiting. It was incised and the clots evacuated, but as there was no active bleeding, packing was deemed unnecessary. She was given chemotherapy in an attempt to avoid infection. On the fifth postpartum day, however, she developed a low-grade fever and discharged a few dark clots per vagina. The fever and discharge resolved by the eleventh postpartum day, and the patient was discharged on the thirteenth postpartum day in good condition. She had no further difficulty, and at the six weeks' postpartum examination no scar could be found in the vagina, and involution was complete.

CASE 3.—Mrs. A. V., a 30-year-old, white, gravida iii, para 0, was admitted to the hospital on March 29, 1947. Prenatal care was adequate. She was given progesterone in the first half of this pregnancy because her previous obstetric history consisted of one spontaneous abortion and one miscarriage at five months of a twin pregnancy. There was no evidence of toxemia. She was admitted to the hospital in active labor with a blood pressure of 110/68, with occiput left anterior, fetal heart tones 138, pains regular and of moderate intensity. Sedation was given, and labor progressed normally, and after thirteen hours and fifteen minutes, following a left mediolateral episiotomy, she delivered spontaneously a six pound, three ounce female infant. The episiotomy was repaired, and the mother was sent to the floor in good condition.

Fourteen hours later, the patient complained of pain in the perineal region on motion. Examination revealed that she was cool, moist, and cyanotic, with a pulse of 120 to 130. A huge hematoma, involving the right side of the labia, vestibule, perineal body, and both buttocks, was found. Immediate treatment consisted of treating the shock and replacing the blood loss. The clots were subsequently evacuated, and, as no bleeding was seen at this time, the hematoma was left to granulate. In the early stages, penicillin and sulfadiazine were

4. *Obstetric Shock*.—A hematoma above the cardinal ligaments, due either to the rupture of a varix in the broad ligament or to pressure necrosis, must be kept in mind and looked for in all cases of so-called obstetric shock.

Treatment

Historically, the treatment of perineal hematomas was expectant. If or when infection occurred, that was the indication for drainage and evacuation of the cavity. This type of management led to many deaths on the basis of sepsis. The next step was the evacuation of the blood as soon as thrombosis was complete, in about forty-eight hours, with the end in view of preventing the sepsis, but waiting long enough to reduce the possibility of secondary hemorrhage. Some men adhere to this type of management. The consensus at present, however, is to evacuate the blood, secure hemostasis of large vessels by ligature or suture ligature, and pack the cavity. In this way, it is conceivable that the dissection along the planes of cleavage be interrupted before the patient suffers the full damage. Light packing of the hematoma cavity, with further tight packing of the vagina and binding of the perineum, seems to yield the best results. Perhaps it would be satisfactory to pack the cavity with hemostatic absorbable sponges.

When dissection is above the cardinal ligaments or the hematoma is limited to the perimetrium, laparotomy is indicated, and hemostasis must be secured in the most effective manner, so that the area is dry before closing of the abdomen. Hysterectomy is frequently necessary.

Of course, supportive therapy, especially the replacement of blood loss, is imperative.

Case Reports

CASE 1.—Mrs. C. N., a 36-year-old, white, gravida vii, was admitted to the hospital Dec. 21, 1945. She had had adequate prenatal care and was admitted at term with moderate pains but no progress. In three hours, the pain had become exceedingly severe, and the obstetrician was called in consultation. Examination at that time revealed a patient screaming like a wounded animal, with an ashen face and a slow pulse of good quality. The bladder appeared greatly distended. The position and presentation were breech right anterior (shown on previous x-ray), fetal heart tones were 150, the bag of waters was bulging and seemed to be under great pressure, the cervix was fully dilated, and the station minus three. A diagnosis of threatened rupture of the uterus was made, and immediate delivery was recommended and carried out as follows: The patient was anesthetized, the bag of waters was ruptured, the head was flexed, and in two or three pains the patient pushed the head into the pelvis, where it could be delivered easily with forceps.

Immediately following the delivery of the baby there was a large bright red clot of about 200 c.c. The ergotrate was given, and the placenta was delivered by simple expression. The patient continued to bleed bright red blood in spite of a hard uterus and an intact cervix. Bimanual examination revealed a large, soft mass, tense and fluctuating, above and anterior to the bladder. The vagina was tightly packed, and the patient was taken to surgery for laparotomy. Shock therapy and replacement of blood were started immediately. At laparotomy, the following were seen: A large hematoma, the size of a grapefruit, on top of the bladder and under the vesicouterine fold of peritoneum; a postpartum uterus about 14 cm. long, and many large varicosities of the right broad ligament. The area of the uterus posterior to the bladder appeared soft, edematous, and infiltrated with hemorrhage. The hematoma was evacuated, and a supracervical hysterectomy was performed. Hemostasis required more than the usual number of sutures; however, the peritoneum was preserved and used in the usual manner over the stump. The postoperative course was uneventful, and the patient was discharged on the thirteenth postoperative day, in good condition.

The interesting features of this case are the question of diagnosis and the pathogenesis of the hematoma. The early picture of threatened rupture naturally put the operator in mind

Two of the cases were of the broad ligament type. In one of these, fever and the presence of a broad ligament mass were noted on the fourth postpartum day. The mass gradually began to subside, and the patient was discharged in good condition on her sixteenth postpartum day. The other broad ligament case was more colorful. The patient was a multipara. A Pituitrin induction was done, employing an initial dose of 3 minims, followed by a second dose of 3 minims, and a third dose of 2 minims. The length of labor was three hours. The patient sustained a high left cervical laceration. This was repaired and a vaginal tamponade inserted. Two hours later a grapefruit-sized hematoma of the left broad ligament was evacuated by laparotomy. The patient made an uneventful recovery. It seems likely that this accident might not have occurred if smaller dosage of Pituitrin had been employed, namely, an initial dose of $\frac{1}{2}$ minim followed if necessary by 1 minim at intervals of 30 minutes.

Dr. Walsh mentioned the importance of proper hemostasis at the time of delivery in the prevention of postpartum hematomas. Cervical tears, irrespective of length, may give rise to only modest external bleeding. It is curious that in only two of the seven maternity hospitals in which I have worked in the last eight years is it part of the obstetric routine in all cases to inspect the cervix following delivery. Yet, in a series of some 3,500 consecutive deliveries reported from the Evanston Hospital in 1936, in 6.3 per cent of the cases there were lacerations which were 3 cm. or more in length. In addition to restoring the functional integrity of the cervix, it is possible that immediate cervical repair might have a bearing upon the later development of high incidence of hematomas.

Despite the possibility of late necrosis, or intrinsic defect in the blood vessels of the perineal area as a cause of hematomas in this region, it seems inescapable that the vast majority result from improper hemostasis at the time of the repair. I wish to show a lantern slide of a method for the repair of episiotomy which answers this objection. Lifting ligatures are employed to make the supporting structures stand out, and the vaginal fingers press the repaired vaginal mucosa toward the operator. By this means the depth of the incision is made easily accessible.

I enjoyed Dr. Walsh's presentation, and believe the subject is deserving of more consideration than it has received in recent years.

DR. W. H. RUBOVITS.—The same general surgical principles usually employed will simplify the matter of prevention and treatment of this type of hemorrhage. By that I mean, that the attitude toward cervical hemorrhage, whether it be obstetric or gynecologic, is much the same. It is self-evident that hemorrhages of the kind described by the essayists are certain to occur but similar hemorrhages occur in most mysterious ways in gynecologic work. In those days when we did more supravaginal hysterectomies, hemorrhages occurred from the cervical stump in a most inexplicable manner and, also, from the vaginal cuff in total hysterectomy. Hemorrhages from these very vascular structures do occur in the operative care of intraligamentary tumors, particularly fibroids, and it is striking that many of these are formidable-looking tumors and shell out of the intraligamentary folds with little or no hemorrhage, whereas operative fatalities in apparently similar cases occur, due to the predisposition of the patient to bleed from some apparent blood dyscrasia or "pseudohemophilia." With these thoughts in mind, I have tried to concentrate on the matter of hemostasis. Our slogan is, it is easier to save blood than to transfuse. It is easier to check bleeding now at the time of delivery or at the time of operation than it will be twelve hours from now. To that end, and finding it difficult often to employ a suitable needle holder in an inaccessible area, such as the extension of an episiotomy into the fornix, involving a large branch of the uterine artery, I use the Deschamps sharp suture carrier. If there is danger to the urinary bladder, it is possible to make a transverse incision, push the bladder out of the way, and by retracting it, and the ureter, one can very quickly use this instrument for the ligation of the formidable bleeding vessel.

DR. WALSH (Closing).—In our third case, the woman with the severe hemorrhages, I believe, had some type of blood dyscrasia. We rechecked but found nothing except that she ran a low-grade anemia.

given to prevent infection of the cavity. When the surfaces showed good, clean granulation, a secondary closure was attempted on the twenty-fourth day post partum, but was only partially successful. It did accomplish, however, the bridging of skin and mucous membrane in some places and shortened the time necessary for epithelialization.

The wound was completely healed in forty-five days, although hospitalization was not required for the full time. The patient has a functional perineum without complaints, but, as further childbearing is contemplated, plastic will be delayed.

Summary and Conclusions

1. Three cases of postpartum perigenital hematomas are presented: one perineal, one vaginal, and one supravaginal.
2. The etiology, pathogenesis, and diagnosis are discussed.
3. A historical review of the treatment is given, and the modern local treatment is discussed.
4. Early incision of the hematoma with ligature or suture ligature of large vessels and packing of the hematoma cavity is the treatment of choice for perineal or vaginal hematomas, while laparotomy is indicated in the supravaginal variety, and hemostasis must be secured before closure of the abdomen, even if a hysterectomy is necessary.

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Discussion

DR. D. N. DANFORTH.—The subject which Dr. Walsh has presented is one which very fortunately is rarely encountered in practice. Its importance, however, is attested by the occasional reports of fatality due to this cause. The active treatment which he has outlined seems very adequate. Two points which he has mentioned I think are deserving of greater emphasis. First is the early diagnosis. The only case of massive hematoma I have seen, one which extended to Poupart's ligament and deep into the left buttock, occurred in a woman who had complained bitterly of "painful stitches" for twelve hours before an adequate rectal examination was made. The second point, which I consider of the greatest importance, is prevention. In the past five years at the Evanston Hospital, there have been twelve postpartum hematomas which were sufficiently troublesome, or large enough, to be dignified by this diagnosis. During this period there were 6,890 deliveries, giving an incidence of 0.6 per cent. Ten hematomas were perineal. None were of the massive type described by Dr. Walsh, although in three cases they were sufficiently large that the mass was incised and evacuated. In one of these, as in Walsh's third case, the accumulation of blood was very obviously due to defective hemostasis at the time of delivery. All of the perineal group were febrile, the elevation first appearing between the third and fifth postpartum days. This was of a low-grade type, reaching up to 101° F. Its consistency in these cases suggests that fever is an important part of the clinical picture, and suggests further that a careful rectal examination may be useful in the diagnosis of unexplained fever during the puerperium.

both. Those who advocate the psychological approach to the problem believe that the cycle can be more rationally interrupted at the place where it begins, in fear, and that this can be done by education. Obviously this may not be easy, because a fear which is part of an environmental pattern may be difficult to dispel. Nevertheless, in most women such fear can be reduced so that pain and discomfort can be eliminated to a degree that a woman is willing and able to accept. In our study we have delivered five women who have steadfastly denied on repeated questioning that they felt anything which could be classified as discomfort. These women were alike only in that they appeared completely fearless during labor.

To state the hypothesis briefly, traditional fear is manifested in labor by tension, and tension generalized and specific is the chief cause of pain in normal labor. Whether this assumption is scientifically correct from the viewpoints of anatomy, physiology, and psychology is not too important if it can be accepted pragmatically. Our experience has taught us that it can, for it works.

Shortly after publicity was given in the lay press to Dr. Grantly Dick Read's work, a young primigravida was admitted to our ward, early in labor, who announced that she wanted natural childbirth without anesthesia. She was completely successful in achieving her desire, much to the great interest of those who attended her. It was not long before other clinic patients expressed a similar desire, an interest which we were glad to encourage. In the six months following the first demonstration we delivered sixteen such women, and the experience was enough to convince the professional and nursing staff that natural childbirth was a very real thing and that it demanded more than casual consideration.

Since an unusual patient-physician relationship seemed to be a primary requisite, and since the technique as described by Dr. Read apparently required a high degree of cooperative intelligence on the part of the patient, we were anxious to determine whether these principles could be applied in a teaching ward obstetric service. It was decided, therefore, to select for study every third patient who registered in the clinic, provided she was no more than twenty-eight weeks pregnant and was deliverable from below. We proposed to apply to this selected group the physiotherapeutic and psychological techniques recommended for natural childbirth. In addition, it was decided to include in the study, also, those women who came to the clinic requesting natural childbirth.

We outlined the procedure to be adapted to these two groups and, in addition to the usual prenatal program, put into operation a conditioning program which is essentially of a dual nature. One aspect of this might be termed the elimination of negative conditioning, and the other the substitution of positive conditioning. The former consists of attempting to change the attitudes and behavior patterns traditional not only in pregnant women, but in hospital attendants of women who are delivered on a teaching ward obstetric service. For example, we have eliminated from our vocabulary the word "pain," always speaking of "contractions." Positive conditioning consists of those procedures which are used in educating the expectant mother to the end that she will enter the labor with an assurance that she is undergoing a normal experience and that

A CLINICAL STUDY OF NATURAL CHILDBIRTH

A Preliminary Report From a Teaching Ward Service

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IT IS not unusual for obstetricians to attend women in labor who have appeared to experience little or no distress. This often is explained on the grounds of stoicism, high multiparity, or high pain threshold. Since the advent of anesthesia great emphasis has been placed on the alleviation of pain in labor, and pain itself has come to be accepted as a normal concomitant. Most obstetricians, however, will agree that emotion does play a large role in pregnancy and labor, and that the woman who is anxious, fearful, and tense at the start of labor will not go through that performance as well as one who has a sympathetic understanding of the situation and accepts it more or less philosophically. In considering this subject, attention must be given to the work of Dr. Grantly Dick Read, of London, who, through his writings and teaching, not only has given an explanation of the cause of pain in childbirth, but has also suggested methods for its prevention in normal labor. He points out that the inner circular muscle layer of the uterus is innervated by the sympathetic nervous system and that it acts as a sphincter in much the same manner as the bladder sphincter. This sphincter action is opposed in the uterus, as in the bladder, by the action of the longitudinal or detrusor muscle, which is innervated by the parasympathetic nervous system. If for any reason the circular sphincterlike muscle and the longitudinal muscle are contracting at the same time, the intrauterine tension will reach a threshold at which the impulses transmitted through the thalamus to the cortex will be interpreted as pain. In physiologic labor this should not occur except possibly at the end of the first stage, when the stretching of the cervix is at its maximum.

Physiologic investigations have shown that in general sympathetic discharge occurs in a state of fear. Fear can cause tension, which in itself causes pain. That fear, to a greater or lesser degree, is present in labor almost universally in our culture is not surprising when we consider the fact that the young woman approaching childbirth not only has acquired a mass of misinformation concerning childbirth, but has also acquired a belief that labor is a painful and terrifying ordeal. This fear usually grows concurrently with the abdomen. One example of this attitude was expressed by one of our patients who, after a natural labor, exclaimed, "Now I know what it is like. I can have another baby without being afraid!"

In the usual conduct of labor the obstetrician attempts to break the fear-tension-pain syndrome by drugs which will produce analgesia or anesthesia, or

not allowed to be alone. Again, through the good auspices of the Maternity Center Association, we are fortunate in having the services of a nurse midwife on our ward service who has been trained in these methods, and she or the regular nursing supervisor, or a delivery service nurse, is with the patient. The physician also sees the patient at proper intervals, especially during certain important periods in the labor. *Third*, the techniques of relaxation are instituted when they become necessary. This usually occurs in the average labor when the external os reaches about 4 cm. dilatation. Ordinarily up to this point the patient is hyperactive and may be mildly euphoric. However, the contractions at this period are apt to be stronger and relaxation techniques usually become necessary. If used too early, these techniques may become tiring in themselves because of the concentrated mental effort necessary to carry them out. At this stage, when the patient assumes the relaxing position and starts abdominal breathing, it is easy to demonstrate to her the effect of such relaxation by the alleviation of her discomfort. This reinforces her confidence and more often than not will allow her to continue to nearly full dilatation without further instruction. When almost full dilatation is reached, the most crucial point in the labor is at hand. The physician should certainly be present at this time. Concurrent with an increased amplitude of the contractions, the patient may complain of a severe backache. This can be relieved by an attendant giving pressure and massage over the sacral region. In addition, the patient needs reassurance that all is going well and that after ten or twelve contractions she will feel better, which actually occurs when the second stage becomes established. When the second stage is started the patient is urged to work with her contractions and to relax between times. As the labor progresses the patient is encouraged to assume a more mechanically advantageous position, which consists in flexing the thighs on the abdomen and the legs on the thighs. The patient is aided in this by attendants, and in this way simulates the squatting position which she has learned in her class work. When the contraction fades away she straightens out her legs and again relaxes. The patient is not placed on the delivery table until delivery is assumed to be about ten or fifteen minutes distant, and she is not placed in stirrups until the last possible moment. Many patients have told us that the position in stirrups destroys the mechanical advantages of the fully flexed position.

We use episiotomy when indicated in primigravidas and multiparas. This can be done in many instances without disturbing the patient at the acme of a contraction, when the head distends the perineum. Patients may not even be aware of its performance. However, infiltration with a local anesthetic may be useful, especially later on during the repair of the incision. As the head is being delivered over the perineum the mother is asked to pant, which she does with ease, and the head is delivered slowly. After the delivery the infant is placed on the sterile drape covering the abdomen and at this point she usually becomes quite euphoric. However, sterile technique is maintained and she is not allowed to touch the baby except through the drapes. When the placenta separates, the mother can usually deliver it without aid. Bleeding is usually minimal, and the third stage is generally very short. As may be expected, the necessity for the use of methods of resuscitation for the infant is so rare as to be practically nonexistent.

Since our study of these methods has been in operation but a relatively short time, the total number of women who have been delivered is limited. At this writing we present a total of 156 deliveries. We feel, however, that our observations in this number have enabled us to reach conclusions that are significant. It is obviously difficult in a study of this nature to be completely objective. Many of the factors which we are attempting to evaluate cannot be measured.

she will be aided by sympathetic and skilled attendants in whom she can have complete confidence. All of the patients in the study, "selected" or "volunteer," are treated essentially as follows. The registration or initial visit follows the usual pattern of history taking, physical examination, laboratory study, and instruction. In addition, an attempt is made to assess the patient's personality, to reassure her as to her physical condition, and to make her feel that the clinic staff of nurses and physicians is taking a real interest in her. She is encouraged to ask questions. On the following visit, in addition to the routine antenatal examination, the patient attends a short lecture on the anatomy and physiology of the female genital tract, information about fertilization, fetal growth, and the explanation of the signs and symptoms of early pregnancy. Patients are told about the effects of tension and the relationship of fear to tension and pain. Diagrams are used as much as possible, and questions are encouraged. During the next visits the patient is taught four exercises which are designed to increase the elasticity and tonus of the back, abdominal, and perineal muscles, and also breathing and position exercises which aid in relaxation. Shortly after inaugurating the program, through the generosity of the Maternity Center Association of New York, we were fortunate in having with us for a short period Mrs. Helen Heardman, of England, a skillful physiotherapist who for the past eight years had been working with pregnant and parturient women. Under her teaching we learned the exercises which are now taught by the physician in charge of the follow-up prenatal examination. This instruction is augmented by classes conducted by a nurse midwife who has been trained also in the use of these physiotherapeutic techniques. Patients are instructed to practice these exercises of regular intervals at home.

At the first visit in the eighth calendar month patients attend a second lecture on the course of labor. The action of the muscles concerned in labor is outlined, the various stages of labor are explained, and the role that the patient should play in each period is explained. Patients are also told about the signs and symptoms of early labor and the hospital admitting routine. At no time during any lecture is the patient told that labor will be painless or that she will receive no anesthesia. Following this second lecture the patient will ordinarily come for about four more clinic visits before delivery. During these she attends exercise classes conducted by a nursing supervisor or a nurse midwife. Mistakes are corrected and labor is rehearsed. Breast massage is started for those who intend to nurse their infants.

If the patients have been properly indoctrinated by this regime, the effect is obvious on their admission to the hospital. They appear calm, confident, and quite ready to undergo an experience which to them seems to be a natural one.

The management of labor in these patients follows a rather definite pattern. We attempt to follow several principles. The *first* is that of keeping the patient informed of her progress. She is told about the position of her baby. She may listen to the fetal heart, and she is informed from time to time of the progress of the baby through the birth canal. The devious explanation, the hushed tones, or the overly sympathetic attitude are studiously avoided. *Second*, the patient is

TABLE I. VOLUNTEER GROUP

| | EXCELLENT | GOOD | FAIR | POOR | TOTAL |
|------------|-------------------|------|------------------|------|-------|
| Primiparas | 20 | 7 | 2 | 0 | 29 |
| Multiparas | 12 | 4 | 2 | 1 | 19 |
| | 32 | 11 | 4 | 1 | 48 |
| | 43 (or 89.58%) | | 5 (or 10.42%) | | |

TABLE II. SELECTED GROUP

| | EXCELLENT | GOOD | FAIR | POOR | TOTAL |
|------------|-------------------|------|-------------------|------|-------|
| Primiparas | 24 | 22 | 11 | 7 | 64 |
| Multiparas | 23 | 14 | 1 | 6 | 44 |
| | 47 | 36 | 12 | 13 | 108 |
| | 83 (or 76.85%) | | 25 (or 23.15%) | | |

TABLE III. TOTAL

| | EXCELLENT | GOOD | FAIR | POOR | TOTAL |
|------------|----------------|------|------------------|------|-------|
| Primiparas | 44 | 29 | 13 | 7 | 93 |
| Multiparas | 35 | 18 | 3 | 7 | 63 |
| | 79 | 47 | 16 | 14 | 156 |
| | 126 (80.7%) | | 30 (or 19.3%) | | |

indoctrination is education. Knowledge replaces ignorance and banishes fear. This is demonstrated by the success of some of our early cases, who had natural childbirth by virtue of their own knowledge of the subject.

Supporting structures are the relaxation techniques and proper attendance during labor. These two are complementary and interdependent. The specific relaxation techniques used are simple and easily taught prenatally. However, in the majority of cases such teaching must be reinforced during labor, when the patient is under stress. This does not mean that it is always necessary for the doctor to spend the entire labor with the patient. We have observed that many patients, usually intelligent, enthusiastic women who have been given a basic minimum amount of prenatal instruction, can go through a labor with little or practically no support. On the other hand, there are some women who without maximum support during labor will become afraid, cease to relax, lose control, and experience pain. We have found that by utilizing especially trained nurses who are adept at teaching relaxation, the physician is free to attend to other duties. If such nurses are not available, the frequent attendance of the physician is a primary requisite. Dr. Blackwell Sawyer, of Toms River, N. J., a pioneer in this country in these methods, emphasizes that the doctor "must be gentle, solicitous, wise, and, above all, he must be present."

In this study we are fortunate in having specially trained nursing personnel available. In addition, the delivery service nurses have been, or are being, trained to carry on these labor techniques.

If a patient is left more or less alone during labor and is expected to endure a process about which she knows nothing and is told nothing, it is not remarkable that she becomes afraid and therefore becomes tense. If the patient is visited frequently by her doctor in whom she has the utmost confidence, who tells her

By means of special records, however, we have attempted to evaluate our results from many points of view. We have tried to study certain aspects of the personality of these patients, to record the indoctrination that they receive, their reaction to it, and to assess the emotional reaction to labor as well as the physical response.

The classification of the end result has been arbitrarily divided in the following grouping:

1. Those labors in which the mother does not ask for or appear to need analgesia or anesthesia are classified as *excellent*.
2. Those labors in which the mother receives a minimum of medication or anesthesia, either because she requests it or seems to need it, are classified as *good*. By minimum is meant a *single dose* of an analgesic such as demerol or seconal given at any time and/or nitrous oxide with contractions at the end of the second stage. *These mothers are fully conscious at delivery.*
3. Those labors in which the mothers appear to receive some benefit from indoctrination but who need a deeper and more prolonged anesthesia are classified as *fair*.
4. Those labors in which the mothers seem to receive no benefit from these techniques, who experience a great deal of pain throughout labor, and in whom the usual amount of analgesia and anesthesia are used, are classified as *poor*.

We also classify the mother's reaction to labor and, in almost all cases where the mother's own appraisal of her experience is at variance with that of the attendants, it has been in the direction of the more successful group.

It is obvious that this classification is arbitrary. Both the "excellent" and "good" group may be said to be successful. This allowance should be made, for the idea that the use of a minimum amount of analgesia and anesthesia constitutes failure must be eliminated. Actually, one can say that exposing patients to the natural childbirth techniques is of definite value in all cases but the "poor" group.

We have compiled various other data and compared such factors as age, physical condition, mental attitude, amount of indoctrination, relaxation, weight of baby, and length of various stages of labor in these patients. As yet the figures show no significant correlation to the techniques, and no positive conclusions can be reached from them. For example, we have not been able to show as yet that the average total length of labor is shortened, nor have we discovered that any single factor will explain success or failure in any individual patient. It seems impossible to predict accurately in any given patient on the basis of any one given characteristic whether or not she will be in the successful group. Our results may be seen in Tables I, II, and III.

From the study of those who have had a poor result, we feel justified in saying that there is a small group of women who cannot achieve natural childbirth. Part of this group is made up of women whom Dr. Read calls unteachable; unteachable because of a lowered intelligence, and are therefore uninterested, or they possess the type of personality which resists teaching or new information of any kind. The rest of this "poor" group is composed of women who have a large degree of subconscious anxiety, particularly centered on childbirth. These women accept the teaching fairly well, but their anxiety becomes evident when labor begins.

As stated before, natural childbirth is primarily based on a physician-patient relationship. The doctor, or doctors, attending the patient must believe in the reality of natural childbirth and must be sympathetic to its aims. Doubt or scepticism on the part of the physician will sooner or later communicate itself to the patient and interfere with a satisfactory result. The keystone of the arch of

The multipara who has had a relatively large number of children and whose intelligence is not of a very high order is usually a poor candidate. In many instances she may have a delivery without undue discomfort without being exposed to indoctrination. In any case, she is hard to evaluate.

In the evaluation of any innovation it is always useful to consider the advantages and disadvantages. Some of the advantages which we have noted are:

1. The majority of labors are spontaneous. Authorities are in universal agreement that obstetric complications, such as frank sepsis, maternal morbidity, hemorrhage, damage to maternal soft parts, fetal morbidity or mortality, especially fetal cerebral damage, have their lowest incidence in spontaneous deliveries and a rising incidence in operative deliveries, in direct proportion to the severity of the operation.

2. The risks attendant on the use of anesthesia are avoided. There is no anesthetic for obstetric use which is 100 per cent safe for mother and baby and which will not have some effect on labor.

3. Another advantage in natural childbirth which, although it has never received much attention, is very real; namely, the psychological advantage. No one who has seen a natural childbirth can doubt that there is established an immediate and close bond between the mother and her baby. This bond, in the opinion of those psychiatrists who have observed it, should and does provide for a mother-child relationship which can have a deep and lasting effect on their mutual adjustment in the distant, as well as the near, future. Many of our natural childbirth patients go from the delivery room to the rooming-in unit, which is organized to promote and study this relationship. The foundations of mental health in the adult are laid in infancy and childhood, and, since infancy begins at birth, we believe that it is reasonable to suppose that, if childbirth is a happy and satisfying experience, the mother-child relationship will have a sound foundation. That it can be a happy and satisfying experience is irrefutable when the mother's reaction is observed. Many multiparas have told us that natural childbirth was far superior to a previous delivery during which they were "knocked out" and didn't know that they had had a baby until the following day. Several have expressed their feeling of closeness to a baby which they felt they had had themselves in contrast to another which had been delivered while they were unconscious.

For purposes of analysis we interview each mother post partum on her reactions to labor. One of the questions we ask is, "Do you want to have your next baby this same way?" We feel that their response is most significant. We have 148 answers to this question:

One hundred twenty-five patients gave an unqualified—yes.

Seven patients gave a qualified—yes—saying that they would if they felt the doctor was sympathetic enough to give them support.

Nine patients gave an unqualified—no. These were all cases who had failed. Seven said they didn't know. Surprisingly enough, of the 125 who answered "yes" to this question, ten had had only fair results, and three had failed completely.

What of the disadvantages?

The usual charge leveled against natural childbirth is that it is unduly time consuming, especially for a private practitioner. We believe that if an additional five minutes were added to each prenatal visit for the purpose of instruction, it would be sufficient for indoctrination purposes. When the patient is in labor more attention by the physician is necessary than usually may be given, but this need not be excessive or unduly demanding. If nurses who are trained in natural childbirth techniques can be utilized, the amount of extra time necessary would be minimal for most cases. This we believe to be of great advantage;

frankly what is going on, if, in addition, she is attended more or less constantly by an understanding nurse who helps her adapt her relaxation exercises to labor, she is usually able to go through without experiencing any more discomfort than she is quite willing to bear.

If, on admission, the history and physical examination indicate that the patient is having a slow labor, or it appears likely that it will be unduly prolonged, the administration of a sedative will often give the patient a period of rest which will be of great advantage. In all cases we are careful not to institute relaxation techniques until the patient needs them. If, in the first stage, when the cervix is about 4-6 cm. dilated, the patient finds it difficult to relax despite adequate instruction, a small dose of analgesic, such as demerol or a barbituate, may be given, always with the suggestion that it will aid relaxation.

It must be emphasized that the end of the first stage is the critical period in almost all natural labors. We have found that it is important at this time to tell the mother that after she passes this period and proceeds into the second stage she will feel better.

As the cervix reaches full dilatation there may be a transient nausea, hiccoughs, or merely a catch in the breath, as the patient inhales slowly. It is our practice at this time to ask the mother to hold the breath after inspiration and to attempt a slight bearing-down effort. If the cervix is actually fully dilated at this time, the mother will immediately remark that this feels better. If, however, she complains that this hurts, vaginal examination, if done, usually will show that the cervix is not completely dilated and that there is still a cervical lip present, which could not be palpated per rectum. If the patient is a primigravida, we do not encourage maximum effort at this time, rather we try to have the patient conserve her strength for the latter part of the second stage.

In "Childbirth Without Fear," Dr. Read emphasizes that we can expect a completely natural childbirth only in a normal labor, and he includes in his criteria for normal labor the proviso that the baby shall be in a vertex presentation, and in an occipitoanterior position. He further states that in occipitoposterior positions the patients will have a severe backache which will cause them to need or want anesthesia. This latter we have observed to be true.

In our 156 patients, we have delivered thirteen in posterior position and four in breech presentation. Five of the posterior positions had excellent results, seven good, and two were complete failures. Of the breech deliveries, two had an excellent result, one good, and one failed completely.

Two of our posteriors were persistent, and because of this we were forced to intervene. In neither of these cases did the mother ask for relief. Operative delivery was elected when progress ceased. In the few cases in which we have found it necessary to intervene, we have used pudendal block, or saddle block anesthesia, believing that these mothers wish to be conscious at the time of delivery, particularly if they have been enthusiastic about natural childbirth.

In analyzing our failures we have uncovered some interesting findings. In all of the patients classified as poor, there was more than one factor present by which the failure could be explained. The predominant factor has usually been deep-seated anxiety, noted after the labor started. In several the anxiety had been manifest in the past, and some of these patients had been treated or seen by psychiatrists. The second factor is often lack of proper indoctrination; the patient has not attended the classes, or has failed to comprehend the teaching, or has not practiced the recommended exercises.

From this we may conclude that a patient with an undue amount of anxiety and who will not accept indoctrination is a poor candidate for natural childbirth. The intelligent woman, however, even though anxiety is present, will be greatly aided.

STUDY OF THE THYMUS IN 7,400 CONSECUTIVE NEWBORN INFANTS*

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THE thymus problem presents today as it has for many decades, a challenge to the physician. Many thoughtful investigators believe that definition and clarification of the physiology of this gland must precede any stable and scientifically sound solution. Controversy has been the keynote of thymus discussion since 1889.

At present there seem to be a few points upon which there is agreement.

1. A competent radiologist experienced in thymus interpretation will usually be able to determine whether the gland is enlarged.¹⁻³

2. Many obstetricians and pediatricians believe that respiratory symptoms in the presence of thymus enlargement justify therapeutic radiation.^{2, 3, 5, 6}

3. In the majority of cases where no other pathology is demonstrable the respiratory symptoms will improve with the rapid thymus atrophy which follows roentgen therapy.⁴⁻⁶

4. There has been no positive proof adduced that sudden death in infants can be due to tracheal compression or bilateral recurrent laryngeal nerve paralysis from enlarged thymus. However, many reliable authorities attest to this possibility and submit autopsy proof of cases which showed no postmortem findings except the presence of an enlarged thymus gland.⁵

5. The general public is thymus conscious and has what is possibly unjustified confidence in the efficacy of roentgen diagnosis and treatment.

The obstetrician has a joint interest with the pediatrician in a solution of this problem because in the early postnatal life of their children parents expect the obstetrician to take whatever measures may be available to forestall future catastrophe. Many obstetricians have delivered babies who were discharged from the hospital in apparent good health and at a later date suddenly died from what was diagnosed as thymus compression. After several such experiences in April, 1938, we began a routine roentgen examination of each newborn infant in an endeavor to prevent such episodes. Over the intervening years we have attempted, in the light of further experience, to modify our technique as seemed conducive toward better results. The material which follows is a presentation of our results from Jan. 1, 1937, to May 1, 1946, comprising a total of 7,391 surviving full-term infants which were delivered at our hospital.

The data were obtained from two sources: first, from the individual infant's chart; second, from a questionnaire addressed to the parents of each child. More detailed information was obtained by telephone contact with all parents who reported thymus enlargement in their children.

*Presented at a joint meeting of the Obstetrical, Gynecological and Pediatric Societies of Pittsburgh, Feb. 3, 1947.

especially in hospital practice it may be the beginning of a new and greatly important development in delivery room nursing service.

Summary

In considering our experience we believe that we are justified in saying that our limited series has shown that natural childbirth is a definite entity which can be taught successfully in a teaching ward obstetric service. We believe that natural childbirth techniques offer decided advantages to mother and child, and are psychologically desirable for most women.

of any other apparent cause for these symptoms, except in Case 3 where they might be attributed to cretinism. All cases showed improvement or recovery after roentgen therapy.

TABLE II. ANALYSIS OF THREE CASES WITH SYMPTOMS AND ENLARGEMENT OF THYMUS FROM GROUP A

| AGE AT ONSET | SYMPTOMS | DIAGNOSIS | THERAPY | RESULTS |
|--------------|-------------------------|-------------------------------------|----------|-------------|
| 1. 3 months | Mild dyspnea | Enlarged roentgen shadow | Roentgen | Recovery |
| 2. 7 months | "Fits of strangulation" | Enlarged roentgen shadow | Roentgen | Recovery |
| 3. 6 weeks | Dyspnea, cough | Enlarged roentgen shadow, cretinism | Roentgen | Improvement |

TABLE II A. ANALYSIS OF THREE CASES WITH SYMPTOMS AND NO ENLARGEMENT OF THYMUS FROM GROUP A

| SYMPTOMS | DIAGNOSIS | THERAPY | RESULT |
|----------------------|-------------------|---------------|-------------|
| 1. Dyspnea | Enlarged adenoids | Adenoidectomy | Improvement |
| 2. Dysphagia | Bronchitis | Bronchoscopy | Death |
| 3. Dyspnea, grunting | Enlarged tonsils | T & A | Recovery |

The above table contrasts cases with similar symptoms satisfactorily explained by other causes. Corrective measures were directed to the cause. We were unable to define exactly the condition in Case 2, but conversation with the parents seemed to establish it as some acute infectious bronchial condition.

TABLE III. GROUP B. ROENTGEN FILM MADE OF THYMUS OF EACH NEWBORN INFANT. ROENTGEN THERAPY OF 450 ROENTGEN UNITS GIVEN OVER ENLARGED THYMUSES IN THREE TREATMENTS. APRIL, 1938, TO JUNE, 1943

| TOTAL INFANTS | REPLIES FROM QUESTIONNAIRE | SYMPTOMS OF THYMUS ENLARGEMENT | ROENTGEN THERAPY TO THYMUS AT BIRTH | DEATHS DUE TO THYMUS |
|---|----------------------------|--------------------------------|-------------------------------------|-------------------------------|
| 4,128 | 1,566 | 9 (0.57%) | 132 | 2 |
| With enlarged thymus at birth by roentgen examination | | | | |
| 172 (4.1%) | 132 | 0 | 132 | 0 |
| With no enlarged thymus at birth | | | | |
| 3,956 | 1,434 | 9 (0.63%) | 0 | 2 |
| | | | | Found dead in bed. No autopsy |

This group represents our initial effort to prevent future thymus difficulty. There are two figures worthy of note. The incidence of later thymus enlargement in this group is 0.63 per cent compared with 1.61 per cent in the control group, or about one to two and one-half. Of one hundred thirty-two infants which showed thymus hypertrophy and received roentgen therapy, none showed symptoms later. In the two cases of sudden death, both babies were found dead in bed with no history of preceding illness. We do not include them in our thymus cases, although they may have been classified as such in the death certificates. No autopsies were held, so the cause of death remains obscure. These cases both occurred in infants who had shown no thymus enlargement and did not receive therapy.

Questionnaire

Dear Friend:

The efficiency of routine x-ray examination of the thymus gland in newborn infants is being checked by conducting a survey of results. Its success depends entirely on your cooperation.

Will you kindly answer the following questions, place this letter in the enclosed envelope, and mail at your earliest convenience.

1. Is your child which was born ----- well now? -----
(date) .
2. Did the child ever have crowing cry, difficulty in breathing or swallowing? -----
3. Did the doctor ever say the child had trouble with the thymus gland? -----
- If the answer to Question 2 or 3 is "yes," please explain.

Group A comprises 728 surviving full-term babies discharged from the hospital between January, 1937, and April, 1938. We have designated this a control series. No roentgenograms were made from these children. The results are illustrated in Table I.

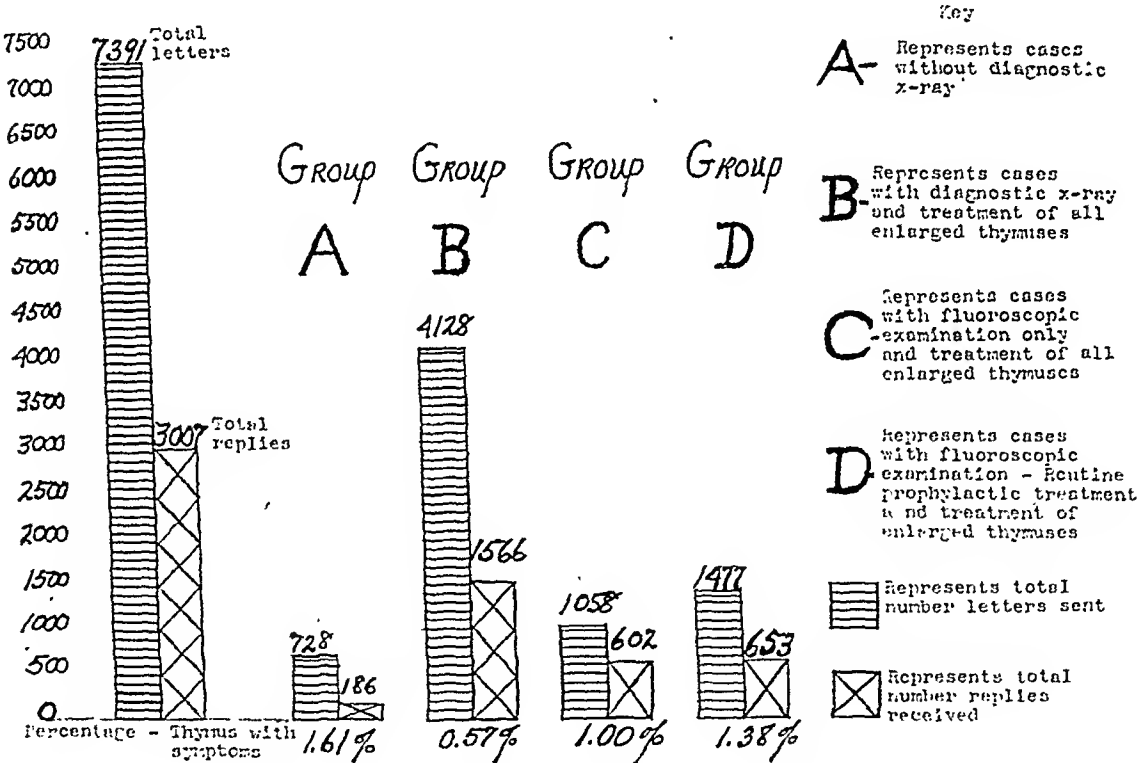


Fig. 1.—Survey, thymus gland, 1937 to 1946.

TABLE I. GROUP A. CONTROL SERIES. NO ROENTGEN EXAMINATION OF THYMUS GLAND

| TOTAL INFANTS | REPLIES FROM QUESTIONNAIRE | SYMPTOMS WITH THYMUS ENLARGE-MENT | ROENTGEN THERAPY TO THYMUS AT BIRTH | DEATHS DUE TO THYMUS |
|---------------|----------------------------|-----------------------------------|-------------------------------------|----------------------|
| 728 | 186 | 3 (1.61%) | 0 | 0 |

We have designated the cases in Table II as thymus cases because they presented symptoms which suggested respiratory obstruction in the presence of thymus enlargement demonstrable by roentgen examination and in the absence

Table IV presents an analysis of nine cases which we have designated as thymus cases by the same criteria previously mentioned. Note that in Case 1 the patient required a tracheotomy at Children's Hospital. All of the patients recovered with roentgen therapy.

Table IV A presents twenty-six cases in which causes other than thymus enlargement were demonstrated. In some of these, roentgenograms showed no enlargement. In Case 5 was another unexplained death which we could not classify because of insufficient data. The patient in Case 15 recovered without treatment, and others recovered after specific treatment. This presents a point stressed by those who maintain that respiratory symptoms even with thymus enlargement are not due to the thymus.

In June, 1943, at the suggestion of Dr. John McCullough, who has done nearly all the radiologic work in this series, we decided to substitute fluoroscopy for diagnostic films. This change was made for several reasons:

1. To make films requires additional expert help to maintain the baby in proper position.
2. Film processing is more time consuming.
3. Fluoroscopy enables the examiner to discount the effect of respiration on the thymus shadow.
4. Differentiation of the thymus from the cardiac and great vessel shadow is easier when using the fluoroscope.
5. Changing the baby's position facilitates estimation of thymus depth in the lateral position.

TABLE V. GROUP C. FLUOROSCOPIC EXAMINATION MADE OF THYMUS OF EACH NEWBORN INFANT. ROENTGEN THERAPY OF 450 ROENTGEN UNITS GIVEN OVER ENLARGED THYMUSES IN THREE TREATMENTS

| TOTAL INFANTS | REPLIES FROM QUESTIONNAIRE | SYMPTOMS OF THYMUS ENLARGEMENT | ROENTGEN THERAPY TO THYMUS AT BIRTH | DEATHS DUE TO THYMUS |
|---|----------------------------|--------------------------------|-------------------------------------|---|
| 1,058 | 602 | 6 (1.00%) | 12 | 1 |
| With enlarged thymus at birth by roentgen examination | | | | |
| 32 (3.02%) | 12 | 0 | 12 | 0 |
| With no enlarged thymus at birth | | | | |
| 1,026 | 590 | 6 (1.02%) | 0 | 1 |
| | | | | (Status thymico lymphaticus and adrenal hemorrhage) |

Table V presents the results in this group. The incidence of thymus enlargement was somewhat smaller than where a film was taken (3.02 per cent to 4.1 per cent). However, more babies presented symptoms with thymus enlargement at a later date (1.00 per cent to 0.57 per cent). It is again notable that twelve cases which received therapeutic x-ray for enlargement had revealed no symptoms when the questionnaire was returned. One baby which was negative upon discharge from the hospital died at six weeks after an illness of several hours. The pediatrician in attendance stated that the baby had none of the symptoms which are suggestive of thymus enlargement, but did have petechiae and purpuric areas which suggested meningitis. Autopsy showed thymus enlargement, general lymphoid hyperplasia, and adrenal hemorrhage. The latter factor precluded its classification as a thymus death.

TABLE IV. ANALYSIS OF NINE CASES WITH SYMPTOMS AND ENLARGEMENT OF THYMUS FROM GROUP B

| AGE AT ONSET | SYMPTOMS | DIAGNOSIS | THERAPY | RESULT |
|--------------|----------------------------|---|--------------------------|------------|
| 1. 4 months | Acute dyspnea | Enlarged roentgen shadow | Roentgen and tracheotomy | Recovery |
| 2. 6 weeks | Crowing cry | Enlarged roentgen shadow | Roentgen | Recovery |
| 3. 6 months | Dyspnea, noisy respiration | Enlarged roentgen shadow | Roentgen | Recovery |
| 4. 2 months | Dyspnea, noisy respiration | Enlarged roentgen shadow | Roentgen | Recovery |
| 5. 10 months | Dyspnea, wheezing | Enlarged roentgen shadow | Roentgen | Recovery |
| 6. 3 weeks | Dyspnea, crowing cry | Enlarged roentgen shadow | Roentgen | Recovery |
| 7. 10 months | Dysphagia, crowing cry | Enlarged roentgen shadow | Roentgen | Recovery |
| 8. 2 weeks | Dysphagia, crowing cry | Enlarged roentgen shadow. Enlarged tonsils | Roentgen tonsillectomy | Recovery |
| 9. 2 weeks | Choking | Enlarged roentgen shadow. Congenital heart | Roentgen | Unrelieved |

TABLE IV A. ANALYSIS OF TWENTY-SIX CASES WITH SYMPTOMS AND NO ENLARGEMENT OF THYMUS FROM GROUP B

| AGE AT ONSET | SYMPTOMS | DIAGNOSIS | THERAPY | RESULTS |
|---------------|---------------------------------|---|---------------|-------------|
| 1. | Crowing cry, dyspnea | Asthma | T & A | Improvement |
| 2. | Wheezing | None | Roentgen | Recovery |
| 3. | Dysphagia | Enlarged tonsils | T & A | Recovery |
| 4. | Dyspnea | Enlarged tonsils | T & A | Recovery |
| 5. | Crowing cry, dyspnea | None | None | Death |
| 6. | Crowing cry, dyspnea | Enlarged tonsils and adenoids, asthma | T & A | Improvement |
| 7. | Crowing cry, vomiting | None | None | None |
| 8. | Dyspnea, dysphagia | Sore throat, cervical adenitis | Symptomatic | Recovery |
| 9. | Crowing cry, dyspnea, dysphagia | None | None | Recovery |
| 10. 3 weeks | Dysphagia, choking | None | None | Recovery |
| 11. | Noisy breathing | Enlarged tonsils. Negative thymus ray | T & A | Recovery |
| 12. | Crowing cry | None | Symptomatic | Recovery |
| 13. | Dysphagia | None | None | Recovery |
| 14. | Dyspnea | None | None | Unrelieved |
| 15. 13 months | Dysphagia, dyspnea, crowing cry | Tracheal obstruction | Tracheotomy | Recovery |
| 16. | Dyspnea, dysphagia | Enlarged tonsils, adenoids. Negative thymus ray | T & A | Recovery |
| 17. | Dyspnea | Enlarged tonsils, adenoids | T & A | Recovery |
| 18. 2 weeks | Dyspnea, cyanosis | Negative thymus ray | None | Recovery |
| 19. | Crowing cry, cough | Negative thymus ray | None | Recovery |
| 20. 1 year | Dyspnea, dysphagia | Enlarged adenoids | Adenoidectomy | Recovery |
| 21. | Dyspnea | None | None | Recovery |
| 22. | Crowing cry, dyspnea, dysphagia | Enlarged tonsils, adenoids | T & A | Recovery |
| 23. 6 months | Wheezing | Asthma | Symptomatic | Unrelieved |
| 24. 4 months | Dyspnea | Negative thymus ray | Roentgen | Recovery |
| 25. 2 months | Crowing cry | None | None | Recovery |
| 26. | Wheezing | Negative thymus ray | Roentgen | Recovery |

of diagnostic fluoroscopy with therapeutic radiation to enlarged thymuses only, beginning June 1, 1946. In addition, a film was taken of the hypertrophied thymuses for comparison, should later examination be necessary, and also for medicolegal purposes.

TABLE VII. GROUP D. FLUOROSCOPIC EXAMINATION MADE OF THYMUS OF EACH NEWBORN INFANT. ROENTGEN THERAPY OF 450 ROENTGEN UNITS GIVEN OVER ENLARGED THYMUS IN THREE TREATMENTS. PROPHYLACTIC THERAPY OF 75 TO 150 ROENTGEN UNITS GIVEN OVER ALL OTHER THYMUSES

| TOTAL INFANTS | REPLIES FROM QUESTIONNAIRE | SYMPTOMS OF THYMUS ENLARGEMENT | ROENTGEN THERAPY TO THYMUS AT BIRTH | DEATHS DUE TO THYMUS |
|---|----------------------------|--------------------------------|-------------------------------------|---|
| 1,477 | 653 | 9 (1.38%) | 653 | 2 |
| With enlarged thymus at birth by roentgen examination | | | | |
| 33 | 11 | 0 | 11 | 1 Dyspnea 2 hours. Death. No autopsy |
| With no enlarged thymus at birth | | | | |
| 1,444 | 642 | 9 (1.40%) | 642 | 1 Sudden death— 3 weeks. Diag- nosed thymus. No autopsy |

Table VII reveals a sharp increase in incidence of symptoms with thymus enlargement over that found where enlarged thymuses received a therapeutic radiation and the normal ones were untreated (1.40 per cent to 1.02 per cent or 0.63 per cent). The incidence approached that where no diagnostic or therapeutic efforts were made (1.61 per cent). This procedure would more accurately be called provocative. The dosage was reduced from 150 to 75 roentgen units when a few infants showed bronzing of the skin of the exposed area.

TABLE VIII

| AGE AT ONSET | SYMPTOMS | DIAGNOSIS | THERAPY | RESULT |
|--------------|---|--------------------------------------|---------------------|--|
| 1. 3 weeks | Dyspnea, dysphagia, harsh cough, wheezing | Enlarged roentgen shadow | Roentgen | Recovery |
| 2. 4 weeks | Cough, noisy breathing | Enlarged roentgen shadow (9 months) | Roentgen | Recovery |
| 3. 3 weeks | Dyspnea | Enlarged roentgen shadow | Roentgen | Recovery |
| 4. 3 weeks | Noisy breathing | Enlarged roentgen shadow (2½ months) | Roentgen | Recovery |
| 5. 1 month | Dyspnea (required oxygen) | Enlarged roentgen shadow | Roentgen | Recovery |
| 6. 3 weeks | Crowing cry, dyspnea 6 months | Enlarged roentgen shadow | Radium | Recovery |
| 7. 7 months | Choking spells | Not confirmed | None | Relieved |
| 8. 2 months | Dyspnea, crowing cry | Enlarged roentgen shadow | Roentgen | Symptoms relieved but recurred at 8 months |
| 9. 2 months | Noisy breathing | Enlarged roentgen shadow | Roentgen and radium | Recovery |

TABLE VI. ANALYSIS OF SIX CASES WITH SYMPTOMS OF ENLARGEMENT OF THYMUS FROM GROUP C

| AGE AT ONSET | SYMPTOMS | DIAGNOSIS | THERAPY | RESULTS |
|--------------|------------------------|---|---------------------|--------------|
| 1. 3 months | Crowing cry | Enlarged roentgen shadow | Roentgen | Recovery |
| 2. 4 weeks | Dysphagia, crowing cry | Enlarged roentgen shadow | Roentgen | Recovery |
| 3. 2 weeks | Dysphagia | Enlarged roentgen shadow (3 months) | Roentgen | Recovery |
| 4. 6 weeks | Dyspnea, crowing cry | Enlarged roentgen shadow | Roentgen at 7 weeks | Recovery |
| 5. 6 weeks | Dyspnea, cyanosis | Autopsy status thymico lymphaticus and adrenal hemorrhage | | Sudden death |
| 6. 2 years | Dyspnea | Enlarged roentgen shadow, congenital heart | Roentgen | Improvement |

Table VI is an analysis of six cases from Group C which showed later thymus enlargement with symptoms after a negative roentgenogram in the immediate postnatal period. Case 6 showed a coincidental congenital heart. However, the respiratory symptoms improved after radiation.

TABLE VI A. ANALYSIS OF TEN CASES WITH SYMPTOMS AND NO ENLARGEMENT OF THYMUS FROM GROUP C

| SYMPTOMS | DIAGNOSIS | THERAPY | RESULT |
|-----------------|----------------------|-------------|-------------|
| 1. Crowing cry, | Croup | Symptomatic | Recovery |
| 2. Dyspnea | Adenoids | Not stated | Recovery |
| 3. Dyspnea | Allergic asthma | Not stated | Improvement |
| 4. Dyspnea | Enlarged tonsils | T & A | Recovery |
| 5. Dysphagia | and adenoids | | |
| 6. Dyspnea, | Enlarged tonsils and | None | Unrelieved |
| dysphagia | cervical glands | | |
| 7. Dyspnea | Enlarged tonsils | None | Unrelieved |
| 8. Crowing cry, | Asthma | None | Recovery |
| dyspnea | Atelectasis | None | Recovery |
| 9. Dyspnea | Tonsillitis | Symptomatic | Improvement |
| 10. Dyspnea, | None | None | Unrelieved |
| dysphagia | | | |

Table VI A presents ten cases from Group C with symptoms apparently due to other causes than thymus hypertrophy. Case 10 was placed in this group despite the absence of a diagnosis, since we were unable to contact the people for more specific information.

In September, 1944, we noted that thymus enlargement with symptoms occurred in babies whose roentgenograms at birth were negative and never in infants whose positive roentgenograms were succeeded by treatment. We decided that our results might be improved by continuing to give a therapeutic dose (450 roentgen units) to thymuses which were enlarged, and by administering a smaller dose (75 to 150 roentgen units) prophylactically to the thymuses that were considered normal.

Table VII presents our results in this Group D.

We knew even before this survey was made that we were hearing of more infants with obstructive respiratory symptoms than had previously been the case. We were so convinced of this that we reverted to our former procedure

3. Groups B and C in which the infants with enlarged thymus shadows received roentgen therapy showed a lower incidence of respiratory symptoms associated with enlarged thymus later. Although the percentage incidence is impressive, a change of only one case in these small groups of nine and six cases would change the picture completely.

4. In group D the incidence of later thymus enlargement with symptoms was higher than in groups B and C. This may indicate that minimal doses of roentgen rays to normal thymuses in the neonatal period are provocative and their use is unwise.

5. Many infants with respiratory symptoms had roentgenograms made of the thymus. Irradiation therapy was given to those in whom an enlarged thymus shadow was seen. Most of these improved. Some infants with the same symptoms and negative roentgenograms improved without therapy; others retain their symptoms.

6. Diagnostic roentgenograms offer some reassurance to parents who are thymus conscious. This is not an undesirable effect. The alleviation of anxiety is a commendable medical achievement.

Conclusions

1. Negative diagnostic thymus roentgenograms in the neonatal period do not preclude the possibility of enlargement with symptoms at a later date.

2. Infants exhibiting symptoms commonly attributed to thymus enlargement should have roentgenograms. If the thymus shadow is enlarged, roentgen therapy is indicated.

3. In many cases respiratory symptoms occur in the absence of an enlarged thymus shadow. If a specific etiological factor is found and treated the results are generally good. If no cause is found and no treatment given, the results are also generally good.

4. The obstetrician or pediatrician should accede to the wishes of parents who want neonatal roentgenograms of their children. It might even be wise to administer therapeutic dosage over the thymus. Whatever assurance is gained by this apparently harmless and perhaps beneficial procedure will aid in alleviating an anxiety which occasionally becomes a thymus phobia.

5. Neonatal roentgenograms have not aided us in forestalling sudden death in young infants. The benefits to be gained by preventing later enlargement with respiratory symptoms in the 5 per cent who show neonatal thymus enlargement does not justify their use as a routine procedure. Patients in these cases can apparently be adequately and safely treated after the onset of their symptoms.

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Table VIII is our analysis of cases showing later symptoms. It is interesting to note that in Case 2 the patient had symptoms from the fourth week, showed enlargement by roentgenogram at nine months, and recovered after treatment. Case 7 was not confirmed by roentgen examination and we were unable to interview the people. In Case 8 the patient had a recurrence of symptoms eight months after treatment. In one, Case 6, the patient was treated by radium, and in another, Case 9, by x-ray-radium combination.

TABLE VIII A. ANALYSIS OF NINETEEN CASES WITH SYMPTOMS AND NO ENLARGEMENT OF THYMUS FROM GROUP D

| AGE AT ONSET | SYMPTOMS | DIAGNOSIS | THERAPY | RESULT |
|--------------|-----------------------|--------------------------------|-------------|------------|
| 1. | Dysphagia | Enlarged thymus | None | Recovery |
| 2. | Dyspnea, crowing cry | Negative thymus ray | None | Recovery |
| 3. | Dyspnea | None | None | Unrelieved |
| 4. | Dysphagia | None | None | Unrelieved |
| 5. | Noisy night breathing | None | None | Unrelieved |
| 6. | Occasional cyanosis | None | None | Recovery |
| 7. | Dyspnea | Acute bronchitis | Symptomatic | Recovery |
| 8. | Dyspnea | Acute bronchitis | Symptomatic | Recovery |
| 9. | Crowing cry, dyspnea | None | None | Unrelieved |
| 10. | Noisy breathing | None | None | Recovery |
| 11. 2 months | Dyspnea | None | None | Recovery |
| 12. 7 months | Dyspnea | Pertussis; negative thymus ray | Symptomatic | Recovery |
| 13. | Dyspnea, dysphagia | Bronchitis | Symptomatic | Recovery |
| 14. | Choking | None | None | Recovery |
| 15. | Crowing cry | Negative thymus ray | None | Recovery |
| 16. 6 months | Dyspnea | Negative thymus ray | None | Recovery |
| 17. | Dyspnea | Asthmatic bronchitis | Symptomatic | Recovery |
| 18. | Dyspnea, crowing cry | None | None | Recovery |
| 19. | Noisy breathing | None | None | Recovery |

Table VIII A analyzes nineteen cases with symptoms and no thymus enlargement from Group D. In Case 1 the patient was stated to have enlargement by a notoriously unreliable individual, with a portable x-ray machine, who did not advise treatment, and the baby recovered uneventfully. Several others had negative roentgenograms. Some had definite other causes for their respiratory embarrassment, and the remainder were undiagnosed, untreated, and are no worse or are recovering (Fig. 1).

Fig. 1 is a summary of the results of our survey to date.

Discussion

1. We are unable to shed any light on the pediatricians' problem in appraising the part that the thymus plays in sudden death in infants. The incidence of this catastrophe in newborns was not reduced by our efforts to forestall it by routine neonatal roentgenograms. Our analyses of the five sudden deaths failed to elicit any proof that they were due to thymus compression. Only one occurred in our hospital, and the autopsy showed purpuric spots and adrenal hemorrhage in addition to thymus enlargement. The pediatrician did not believe the symptoms could be ascribed to the latter condition. The other four cases were glibly diagnosed as thymus deaths by a physician or coroner without autopsy.

2. All of the respiratory symptoms with thymus enlargement reported in the questionnaire groups B, C, and D were from children who had normal thymus roentgenograms in the neonatal period.

under the age of 17 or past the age of 39 years and these were eliminated from this study for obvious reasons. This left 2,833 records on patients from 17 through 39 years who are known to have been nongravid and who consulted the office for various gynecic complaints. In this group, there were 1,291 patients who gave as their chief complaint some disturbance in amount, duration, or periodicity of the menses. In this group, 416 patients complained of amenorrhea or oligomenorrhea. Of this selected group, 78 were shown at the initial visit or subsequently proved to have some demonstrable organic lesion to explain the absence, delay, or cessation of their menstruation. This left a group of 338 patients who could be classified as functional amenorrhea or functional oligomenorrhea. It is presumed that some of these patients had organic disease which was neither diagnosed at the initial visit nor diagnosed subsequently. There were 296 patients with amenorrhea or oligomenorrhea on whom the records are complete and the results reported here are based on a study of this group. Others could not be followed or refused treatment.

On the basis of the above statistics, it can be said approximately 45 per cent of the patients from 17 to 40 years of age consulting a gynecologist in private practice have as their chief complaint some disturbance in menstruation. In about 12 per cent, the chief complaint is amenorrhea or oligomenorrhea of a functional nature, using the criteria for diagnosis which this observer deems adequate.

Primary Amenorrhea

Forty-seven patients with primary amenorrhea varied in age from 17 to 34 years. When the menses failed to appear by the seventeenth birthday, the patient was classified as having primary amenorrhea. Endometrial biopsies were obtained on 18 of these patients and a proliferative phase endometrium was found in all. The tissue varied from the very thin atrophic type, found in three patients, to a marked cystic hyperplasia which was demonstrated in two patients. One of the latter group was the oldest patient in the series, namely, 34 years of age. All other biopsies showed the usual persistent proliferative phase with straight tubular glands, compact stroma, and a minimal degree of vascularization.

The secondary sex characteristics were poorly developed in four patients. One of these showed practically no mammary development, a minimal amount of hirsutism and complete absence of the usual female fat distribution. The majority of these patients, however, showed relatively normal development of the secondary sex characteristics and on gross examination could not have been differentiated from normally menstruating women.

Results of Treatment

(a) *Stilbestrol-Progesterone Therapy*.—There were 17 patients in this group seen from Jan. 1, 1940, through Dec. 31, 1944, who were treated with cyclic stilbestrol-progesterone therapy. The earlier cases received 5 mg. stilbestrol daily for twenty days and 5 mg. progesterone daily for the last five days of stilbestrol therapy. Treatment was then discontinued until the onset of the first induced bleeding episode. The twenty-day treatment with stilbestrol-progesterone was then resumed according to the same schedule, the treatment being started on the fifth day of the induced cycle. Stilbestrol was administered in a 5-mg. dose daily from the fifth through the twenty-fifth day of the cycle; progesterone in 5-mg. dose was given from the twentieth through the twenty-fifth day of the cycle. Uterine bleeding occurred in eight patients within six days after completing the first twenty-day treatment course. In all patients who menstruated after the first cycle of treatment, the bleeding recurred during the three consecutive cycles of treatment. Cyclic menstruation continued in only 5 patients

AMENORRHEA AND OLIGOMENORRHEA, ETIOLOGY AND TREATMENT

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WHEN menstruation fails to occur by the seventeenth year of life the condition may be defined as primary amenorrhea. Menstruation having once occurred, followed by cessation for a period of three months, may be defined as secondary amenorrhea. Oligomenorrhea is a convenient term for designating the long-interval type of menstrual cycle, in which the cycle is prolonged from forty days to three months. Menses occurring in a cycle of 24 to 39 days may be considered within the physiologic range. Functional alterations only are under consideration here and cessation or absence of menses due to the menopause, anatomic defects, pregnancy, castration, hysterectomy or masculinizing tumor are not considered. Occurrence of regular cyclic menstruation between the ages of 14 and 40 usually implies a normal pituitary-ovarian-endometrial physiology and deviation from it suggests, but does not necessarily imply, some defect in endocrine physiology.

Sex physiology has for its ultimate purpose the procreation of the species. The complex pituitary-ovarian-endometrial system with the many tangential influences, intrinsic and extrinsic, acting upon it, is designed for the purpose of cyclically maturing a potentially fertile ovum and the preparation of the endometrium for its nidation. Until recently we have taught that menstruation in itself served no useful function. Some doubt is cast upon this concept, however, by recently published work which has demonstrated the presence of a highly toxic englobulin fraction in the menstrual discharge. Clinically, it is well known that delayed menstruation is associated with nervousness, irritability, breast fullness, lower abdominal pain, a syndrome to which has been given the term "menstrual molimina." It is shown in this study that amenorrhea and oligomenorrhea are associated with ovulation failure in a relatively high percentage of patients and endometrial defects other than those associated with ovulation failure are occasionally encountered. Fertility of these patients is impaired and the incidence of spontaneous abortion is approximately three times that observed in cyclically menstruating women. The data to support these statements will be presented in a subsequent report. From this brief résumé, however, it may be assumed that the induction of cyclic menstruation is desirable from a psychological standpoint, necessary for the patient's well-being, and an important adjunct to the treatment of sterility in the female.

Material

Records from Jan. 1, 1940, through Aug. 31, 1947, have been reviewed. There were 4,251 patients who consulted or were referred to an office in which the practice is limited to gynecology and obstetrics. Of this group, 1,001 were known or subsequently proved to be pregnant. There were 417 patients either

months. There were seven patients in whom the amenorrhea occurred following pregnancy and in one case there was a severe hemorrhage at delivery with signs of pituitary failure after delivery. Three cases developed an amenorrhea following a severe febrile illness, in others no demonstrable cause was apparent. Biopsies are available for study on seventy-two patients in this group, the number varying from one to six on each patient. Prior to treatment, sixty-five patients had a persistent proliferative phase and seven showed a persistent secretory phase upon repeated biopsies. Those patients having a proliferative phase varied from moderate atrophy in eleven cases to cystic hyperplasia in twelve cases. In the group of patients with a secretory phase endometrium, there was a history of normal fertility in four patients, while in the much larger group with proliferative phase endometriums there was a history of pregnancy in only nine patients. It is presumed that secondary amenorrhea associated with a secretory phase endometrium is the result of persistent corpus luteum activity. When the corpus luteum fails to undergo atresia there is no estrogen-progesterone withdrawal and menstruation fails to occur.

The secondary sex characteristics were well developed in all patients in this group. There was a marked hirsutism in two cases, but the family history in both supported the conviction that this was on a genetic basis.

Results of Treatment

(a) *Stilbestrol-Progesterone Therapy*.—There were 20 patients in this group seen from 1941 through 1945 who were treated with some form of cyclic stilbestrol-progesterone therapy. The estrogen was administered from the fifth through the twenty-fifth day of the cycle in varying doses and progesterone was administered on various dose schedules between the fifteenth and twenty-fifth days of the cycle. Although the treatment schedules varied somewhat in the type and dose of progesterone used, the essentials of the cyclic sterol treatment were preserved in all during this period. It was observed that uterine bleeding occurred in fourteen patients within six days after completing the first twenty-day treatment course and all of these were in that group which had a proliferative phase endometrium at the onset of the treatment. In no patient with a secretory phase endometrium (four patients) did uterine bleeding follow treatment. In the fourteen patients who bled after the first course of treatment, the cyclic treatment was carried on for three consecutive months, during which time cyclic uterine bleeding was established in all fourteen. A follow-up 3 months after treatment revealed that ten patients (50 per cent) continued to menstruate on a cycle of 26 to 38 days after completing three months of treatment. The other 50 per cent lapsed into their former amenorrheic state. In the group that continued to have cyclic bleeding for three months (ten patients) after discontinuing treatment, there were four who, by biopsy, were shown to be menstruating from a secretory phase endometrium. This gave an ovulation salvage of 20 per cent for the entire group treated with cyclic stilbestrol-progesterone therapy.

(b) *Ethinyl-Estradiol-Progesterone Therapy*.—During the years 1945 and 1946, the treatment schedule was standardized, using 0.3 mg. ethinyl-estradiol daily from the fifth through the twenty-fifth day of the cycle and 5 mg. progesterone daily from the twentieth through the twenty-fifth day of the cycle. There were twenty-six patients so treated. Of this group, twenty had a proliferative phase endometrium and six had a secretory phase endometrium before treatment. Cyclic uterine bleeding was established in twenty patients while under treatment, and all of these were in the group having a proliferative phase endometrium before treatment. In only two patients with a secretory phase endometrium did uterine bleeding occur while under treatment and in these the

for as long as three months following cessation of treatment and only two of these menstruated from a secretory-phase endometrium, indicating that ovulation had followed as a result of, or concomitant with, the treatment in only two patients out of seventeen. The others in the group lapsed either into a completely amenorrheic phase or continued to have long-interval uterine bleeding from a proliferative phase endometrium. Cyclic bleeding was established in 29 per cent of the group for a period of three months after completing treatment, ovulation salvage was 12 per cent.

(b) *Ethinyl-Estradiol-Progesterone Therapy*.—During the years 1945 and 1946, there were 13 patients with primary amenorrhea who were treated on cyclic sterol schedule using 0.3 mg. ethinyl estradiol daily from the fifth through the twenty-fifth day of the cycle and 5.0 mg. progesterone on the twentieth through the twenty-fifth day of the cycle. Endometrial biopsies were done on eight of these patients; all had a persistent proliferative phase. It was observed that these patients tolerated the treatment with less nausea and fewer side reactions than the stilbestrol-treated group. The incidence of estrogen-progesterone withdrawal following the first twenty-day course of treatment was better than that observed in the stilbestrol group; ten patients showed evidence of bleeding within five days after completing the first twenty-day period. Treatment with ethinyl-estradiol-progesterone was continued for 3 consecutive treatment periods in the ten patients who menstruated following the first course of treatment. In one patient, a second course was instituted even though the first was not followed by bleeding, but in this case the second course of treatment did not accomplish that which the first had failed to do. In all patients who menstruated following the first course, cyclic menstruation continued during the three months of treatment. After completing three months of ethinyl-estradiol-progesterone therapy, seven patients continued to have cyclic menstruation for at least three months. Of this group, five patients menstruated from a secretory phase endometrium; three lapsed into an amenorrheic phase or continued to menstruate at long and irregular intervals from a proliferative phase endometrium. Cyclic bleeding was established in 54 per cent for a period of at least three months after completing treatment, and the ovulation salvage was 39 per cent.

(c) *Prometron*.—During the year 1947, 17 patients suffering from primary amenorrhea were treated by the intramuscular injection of Prometron, a mixture containing 2.5 mg. of estradiol benzoate and 12.5 mg. of progesterone in 1 c.c. of sesame oil. This was administered daily for two days immediately after the diagnosis had been established. Patients in this group varied in age from 18 to 32 years. Endometrial biopsy was obtained on 9 of these patients before treatment and all were found to have a persistent proliferative phase. All patients were seen one week after completing the two-day treatment course and in only one did uterine bleeding occur; this was on the sixth day after completion of treatment. Four of these patients were subjected to a second course of treatment and in none did uterine bleeding appear within a week after completing the course. The one patient who did have uterine bleeding after the initial treatment was given another two-day course on the twenty-fifth and twenty-sixth day of the induced bleeding cycle and menstruation was again induced. It may be assumed that two days of treatment with Prometron in a group of patients with primary amenorrhea is followed by no cyclic bleeding and no ovulation salvage.

Secondary Amenorrhea

Patients who had formerly menstruated, but in whom a period of amenorrhea for three months or more had supervened were so classified. There were 94 patients in this group whose ages varied from 22 to 37 years. The shortest period of amenorrhea was three months and the longest interval seventy-three

(b) *Ethinyl-Estradiol-Progesterone Therapy*.—During the years 1945 and 1946, the treatment schedule was standardized, using 0.3 mg. ethinyl-estradiol from the fifth through the twenty-fifth day of the cycle, and 5 mg. progesterone from the twentieth to the twenty-fifth day of the cycle. There were 48 patients so treated. Of this group, forty had a proliferative phase endometrium and eight had a secretory phase endometrium before treatment. Cyclic uterine bleeding was established in 75 per cent (thirty-six patients) while under treatment and all of these were in the group having a proliferative phase endometrium. Cyclic uterine bleeding persisted for a period of at least three months in 67 per cent of these patients after treatment was completed. The study of the endometrium at follow-up examination revealed that 58 per cent menstruated from a secretory phase endometrium, as compared with 35 per cent in the group treated with stilbestrol-progesterone, a presumptive ovulation salvage of 58 per cent in the ethinyl-estradiol group, as compared with 35 per cent in the stilbestrol group.

(c) *Prometron Therapy*.—During the months from September, 1946, through August, 1947, twenty-three patients with oligomenorrhea have been treated with 1 c.c. Prometron daily for two days. There were eighteen patients with a proliferative phase endometrium and five with a secretory phase. Fourteen patients (60 per cent) had uterine bleeding within six days after the second injection and all of those in whom uterine bleeding was induced had a proliferative phase endometrium before treatment. Cyclic Prometron therapy was begun in these patients, giving them the injection on the twenty-fourth and twenty-fifth days of the induced cycle; such treatment was given for three consecutive months. During treatment, 43 per cent of the total number in this group had cyclic uterine bleeding. Only 6 per cent continued to menstruate cyclically for three months after treatment was discontinued, however, and none of these menstruated from a secretory phase endometrium. It is apparent that Prometron was capable of inducing menstruation in 43 per cent of patients in the oligomenorrhea group while under treatment but only 6 per cent of the group were permanently benefited by treatment.

Summary

Approximately 45 per cent of all patients between 17 and 40 years of age consulting a gynecologist in private practice have as their chief complaint a disturbance in the amount, duration, or periodicity of the menstrual cycle. Amenorrhea or oligomenorrhea of a functional nature occurs in 12 per cent of all patients. Primary amenorrhea was invariably associated with a proliferative phase endometrium in every patient seen by this investigator. Secondary amenorrhea was associated with a proliferative phase endometrium in 85 per cent of patients and oligomenorrhea was so associated in 79 per cent. Those patients of the secondary amenorrhea and oligomenorrhea groups who had a secretory phase endometrium had a consistently poor response to any therapy directed toward establishing cyclic bleeding.

Treatment

All patients with amenorrhea or oligomenorrhea were treated by one of the following three treatment schedules:

(a) *Stilbestrol-Progesterone Therapy*.—This consisted of 5 mg. stilbestrol daily for 20 days orally and 5 mg. progesterone on the last five days of stilbestrol therapy. Cyclic treatment of this type was administered for three consecutive months, beginning on the fifth, and ending on the twenty-fifth, day of the cycle.

bleeding had no relation to the schedule of treatment. Cyclical uterine bleeding persisted for a period of at least three months in 61 per cent (sixteen patients) after treatment was discontinued. A study of the endometria from these patients some months after concluding the three-month treatment schedule revealed that 31 per cent (eight patients) were menstruating cyclically from a secretory phase endometrium as compared with a 13 per cent ovulation salvage in the group treated with stilbestrol.

(c) *Prometron Therapy*.—During the months from September, 1946, through August, 1947, 48 patients with secondary amenorrhea have been treated with Prometron, 1 c.c. daily for two days. Twenty-one patients had uterine bleeding within six days after the second injection and each of these patients had a proliferative phase endometrium prior to the onset of the treatment. In none of the eight patients with a secretory phase endometrium before treatment did bleeding occur. Each of the successfully treated patients received another two-day course of treatment on the twenty-fifth and twenty-sixth days of the induced cycle and uterine bleeding occurred in all. The treatment was repeated for a third consecutive month. Six patients menstruated again without treatment within thirty-five days of the last induced bleeding episode, all the others lapsed into their previous state of secondary amenorrhea. In no case of induced uterine bleeding with Prometron did the patient menstruate from a secretory phase endometrium following treatment. In summary, cyclic bleeding was established in 58 per cent while under treatment, 13 per cent continued to have cyclic bleeding after treatment was completed. There was no ovulation salvage.

In the eight patients of this group who had a secretory phase endometrium before treatment, none had uterine bleeding following the administration of Prometron.

Oligomenorrhea

There were 155 patients with oligomenorrhea treated between Jan. 1, 1940, and Aug. 31, 1947. These patients varied in age from 17 to 35 years. Prior to treatment, endometrial biopsies were obtained on 111 of these patients and a proliferative phase was found in 98 and a secretory phase in 13. In the proliferative phase group, there were six with marked hyperplasia and ten who showed atrophy. In twenty-two patients, the long interval menstruation dated from a pregnancy, abortion, or full-term delivery, in thirteen the menstrual difficulty began following a severe febrile illness. Marked obesity was associated in three and extreme emaciation in one.

Results of Treatment

(a) *Stilbestrol-Progesterone Therapy*.—There were 84 patients treated with stilbestrol-progesterone cyclic therapy. The great majority of cases received 5 mg. stilbestrol daily for twenty days and 5 mg. progesterone daily for the last five days of stilbestrol therapy. The others were treated on varying dose schedules, but the essential features of cyclic steroid therapy were preserved in all. There were 218 biopsies on 68 patients in this group, biopsy being taken before and after treatment and at the follow-up examination three months after completing the treatment. Uterine bleeding occurred within six days in 81 per cent (eighteen patients) who had a proliferative phase endometrium at the onset of treatment. No patient with a secretory phase endometrium had bleeding following the twenty-day treatment course. Cyclic bleeding was established in 81 per cent of this group during the three months of treatment. Follow-up examination three months after concluding treatment showed that 68 per cent of the entire group continued to have cyclic menstruation and, of these, 36 per cent bled from a secretory phase endometrium. This provided a presumptive ovulation salvage for the entire group of 36 per cent.

months after treatment was discontinued in 50 per cent. There was an ovulation salvage of 20 per cent.

Ethinyl-Estradiol-Progesterone Therapy.—Cyclic uterine bleeding was established in 79 per cent while under treatment and persisted for a period of three months after treatment was discontinued in 61 per cent. Ovulation salvage was 13 per cent.

Prometron Therapy.—Cyclic uterine bleeding was established in 58 per cent while under treatment and 13 per cent continued to have cyclic bleeding three months after treatment was completed. There was no ovulation salvage.

OLIGOMENORRHEA.—

Stilbestrol-Progesterone Therapy.—Cyclic bleeding was established while under treatment in 81 per cent and persisted for a period of three months after completing treatment in 68 per cent. Ovulation salvage was 36 per cent.

Ethinyl-Estradiol-Progesterone Therapy.—Cyclic uterine bleeding was established while under treatment in 86 per cent and persisted for a period of three months in 67 per cent. Ovulation salvage was 68 per cent.

Prometron.—Cyclic bleeding was established while under treatment in 43 per cent, but only 6 per cent continued to menstruate cyclically for three months after treatment was discontinued. There was no ovulation salvage.

It may be concluded that the most satisfactory treatment for amenorrhea and oligomenorrhea, judged from the standpoint of ovulation salvage or the establishment of cyclic uterine bleeding, is the three months' cyclic administration of ethinyl-estradiol-progesterone according to the plan described. The most convenient form of therapy, where ovulation salvage is not an objective, is to be found in the daily injection of a mixture of estradiol and progesterone over a period of two days. The latter must be considered only as symptomatic treatment. It cannot be recommended on the basis of known gynecic physiology, for the young woman who is amenorrheic is in need of more than palliative treatment. Her capacity to reproduce is at stake. Nothing less than the best therapy known should be advised and cyclic estrogen-progesterone administration is the best available at present.

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(b) *Ethinyl-Estradiol-Progesterone Therapy*.—This consisted of 0.3 mg. ethinyl-estradiol daily for twenty days orally and 5 mg. progesterone intramuscularly on the last five days of ethinyl-estradiol administration. Cyclic treatment of this type was carried on for three consecutive months beginning on the fifth, and ending on the twenty-fifth, day of the induced bleeding episodes.

(c) *Prometron Therapy*.—Mixed estradiol benzoate, 2.5 mg., and progesterone, 12.5 mg., in sesame oil was administered intramuscularly daily for two days. The treatment was carried on for three consecutive months, administering the mixed hormones on the twenty-fourth and twenty-fifth days of the induced bleeding episode.

In order to evaluate each type of treatment as regards its ability to induce withdrawal bleeding, establish cyclic bleeding while under treatment, induce cyclic bleeding for a period of three months following treatment, all patients were divided into three groups, viz., primary amenorrhea, secondary amenorrhea, and oligomenorrhea. There were 568 endometrial biopsies taken, as noted in the body of this paper. They were used as a means of classification and diagnosis, as well as to evaluate the effects of treatment, particularly in regard to ovulation salvage. It was observed that all patients with amenorrhea or oligomenorrhea who had secretory phase endometria at the onset of treatment failed to respond to any type of cyclic steroid therapy. It may be assumed that failure to menstruate in these patients is a result of persistent corpus luteum activity and that the endometrium, already under the influence of estrogen-progesterone, does not respond to any additional stimulation. The degree of endometrial atrophy or hypertrophy, as well as her past history, has a definite relationship to the patient's response to treatment. Patients with marked atrophy of the endometrium responded less well than those with normal or hyperplastic tissue. That ovulation failure was usually associated with amenorrhea or oligomenorrhea is supported by the fact that 86 per cent of the patients had a proliferative phase endometrium prior to treatment.

Conclusions

PRIMARY AMENORRHEA.—

Stilbestrol-Progesterone Therapy.—Cyclic bleeding was established in 48 per cent of patients while under treatment and persisted in 29 per cent for a period of three months after completing treatment. The ovulation salvage for the entire group was 12 per cent following three months of consecutive treatment.

Ethinyl-Estradiol-Progesterone Therapy.—Cyclic bleeding while under treatment was established in 79 per cent and persisted for a period of three months after discontinuing treatment in 54 per cent. The ovulation salvage was 39 per cent after three consecutive months of treatment.

Prometron Therapy.—Cyclic bleeding was established while under treatment in 6 per cent and persisted for a period of three months after discontinuing treatment in no patients. There was no ovulation salvage after three consecutive months of treatment.

SECONDARY AMENORRHEA.—

Stilbestrol-Progesterone Therapy.—Cyclic bleeding was established while under treatment in 70 per cent of patients and continued for a period of three

TABLE I. VARIATION IN SKIN POTENTIAL DIFFERENCES IN NORMAL WOMEN

| ACTIVE ELECTRODE | INDIFFERENT ELECTRODE | P.D. RANGE (M.V.) |
|--|-----------------------------|----------------------|
| 1. Anterior surface of arm | | |
| Distal phalanx, index finger | Mid phalanx, index finger | -10 to plus 15 |
| Mid phalanx, index finger | First phalanx, index finger | -15 to -5 |
| First phalanx, index finger | Center, palm | -5 to plus 16 |
| Center, palm | Center, wrist | -25 to 0 |
| Center, wrist | Center, mid forearm | -25 to -5 |
| Center, mid forearm | Center, antecubital fossa | -15 to plus 12 |
| Center, antecubital fossa | Center, mid arm | -8 to 0 |
| Center, mid arm | Tip of acromion | 0 to plus 5 |
| Tip of acromion | Sterno-clavicular joint | 0 to 0 |
| Distal phalanx, index finger | Distal phalanx, thumb | -10 to 0 |
| Distal phalanx, third finger | Distal phalanx, thumb | -7 to plus 5 |
| Distal phalanx, fourth finger | Distal phalanx, thumb | -5 to plus 3 |
| Distal phalanx, fifth finger | Distal phalanx, thumb | -7 to plus 3 |
| Distal phalanx, index finger | Tip of acromion | -30 to -23 |
| 2. Posterior surface of arm | | |
| Distal phalanx, index finger | Mid phalanx, index finger | -18 to plus 2 |
| Mid phalanx, index finger | First phalanx, index finger | -12 to plus 5 |
| First phalanx, index finger | Center, dorsum of hand | -20 to plus 5 |
| Center, dorsum of hand | Center, dorsum of wrist | -10 to plus 4 |
| Center, dorsum of wrist | Center, mid forearm | -13 to plus 2 |
| Center, mid forearm | Tip of olecranon | 0 to plus 2 |
| Tip of olecranon | Center, mid arm | -5 to plus 5 |
| Center, mid arm | Tip of acromion | plus 1 to plus 1 |
| Tip of acromion | Tip, seventh cervical spine | -2 to 0 |
| Distal phalanx, index finger | Distal phalanx, thumb | -15 to plus 5 |
| Distal phalanx, third finger | Distal phalanx, thumb | -20 to plus 15 |
| Distal phalanx, fourth finger | Distal phalanx, thumb | -5 to plus 2 |
| Distal phalanx, fifth finger | Distal phalanx, thumb | -5 to 0 |
| Distal phalanx, index finger | Tip, seventh cervical spine | -23 to -20 |
| 3. Anterior surface of lower extremity | | |
| Distal phalanx, first toe | Proximal phalanx, first toe | -9 to plus 6 |
| Proximal phalanx, first toe | Center, ankle | -5 to -4 |
| Center, ankle | Center, leg | -15 to -15 |
| Center, leg | Center, patella | -15 to plus 10 |
| Center, patella | Center, mid thigh | -4 to plus 5 |
| Center, mid thigh | Center, inguinal fold | -18 to -5 |
| Medial malleolus | Umbilicus | -19 to -9 |
| Distal phalanx, second toe | Distal phalanx, first toe | -5 to plus 10 |
| Distal phalanx, third toe | Distal phalanx, first toe | plus 3 to plus 18 |
| Distal phalanx, fourth toe | Distal phalanx, first toe | plus 10 to plus 10 |
| Distal phalanx, fifth toe | Distal phalanx, first toe | 0 to plus 13 |
| 4. Right nipple | Right scapula | -5 to -3 |
| Left nipple | Left scapula | -5 to 0 |
| 5. Anterior surface of arm | Posterior surface | |
| Distal phalanx, index finger | | -15 to -1 |
| Middle phalanx, index finger | | -23 to 0 |
| Proximal phalanx, index finger | | -20 to -5 |
| Mid portion, hand | | -40 to -3 |
| Center, wrist | | -15 to 0 |
| Center, forearm | | -12 to 0 |
| Center, elbow | | -20 to 0 |
| Center, mid arm | | -4 to 0 |
| | | -3 to plus 9 |
| 6. Right side of body to left side of body | | |
| Distal phalanx, index finger | | -3 to plus 9 |
| Wrist | | -3 to plus 1 |
| Elbow | | -2 to plus 6 |
| Patella | | -2 to plus 2 |
| Dorsum of ankle | | -1 to plus 8 |
| Scapula | | -1 to plus 1 |
| Nipple, breast | | -1 to plus 1 |

OVULATION STUDIES WITH DIRECT CURRENT POTENTIALS*

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THE literature in the field of bioelectric phenomena has reached considerable proportions, with Lund's recent monograph¹ containing a bibliography of more than fourteen hundred references. This investigation is primarily concerned with some clinical applications of the determination of standing direct current potentials. For consideration of the mechanism whereby electric potentials are generated by living cells, the detailed studies of Osterhout,² Lund,¹ and Beutner³ should be consulted. In general, with suitable instrumentation, a potential difference between the surface of various epithelial structures or even between microscopic areas on the surface of single cells can be detected. Lund and his co-workers¹ have presented a large volume of careful evidence as to the importance of surface potentials in affecting the direction and rate of plant growth. In mammals, measure of potential differences has been used as an index of ovulation,⁴ to chart the rate of wound healing,^{5, 6} to map denervated areas,⁷ in the diagnosis of carcinoma of the cervix,⁸ and to indicate tissues with a relatively high probability of becoming malignant.⁹

Method

The Schorr-Lampert millivoltmeter¹⁰ with a ten megohm input impedance was used. This large input impedance should preclude correction for skin resistance but recent investigations suggest that areas of sympathectomized skin may develop resistances of the order of five megohms. The exploring electrodes were of the type recommended by Burr,¹¹ consisting of coils of Ag-AgCl₂ sealed in a segment of glass tubing whose open end was obturated by a small sponge. The tube was filled with boiled normal saline solution to avoid bubbles. For skin and mucosal surfaces, the electrodes were held by hand and lightly touched to the test area, avoiding any pressure which would squeeze the sponge excessively and change the electrical conduction of the saline bridge.

Findings

Human Skin Potential Patterns.—It must be emphasized that potential difference (P.D.) is being measured and the location of both electrodes is of importance. In a group of six normal women, potential differences between various areas of skin was determined during the intermenstrual period. The diameter of the electrode contact with the skin was 3 mm.

Table I indicates the range of variation in P.D. between various parts of the skin surface. This may be as high as 40 mv. The skin of distal portions of an extremity tends to be electronegative to that of more proximal portions and that of the anterior surface of the upper extremity is always electronegative to the skin of the posterior surface at the same level. The skin of symmetrical portions of the body revealed relatively small potential differences, less than 10

*This investigation was enabled by a grant furnished by the Joseph and Helen Yeamans Levy Foundation.

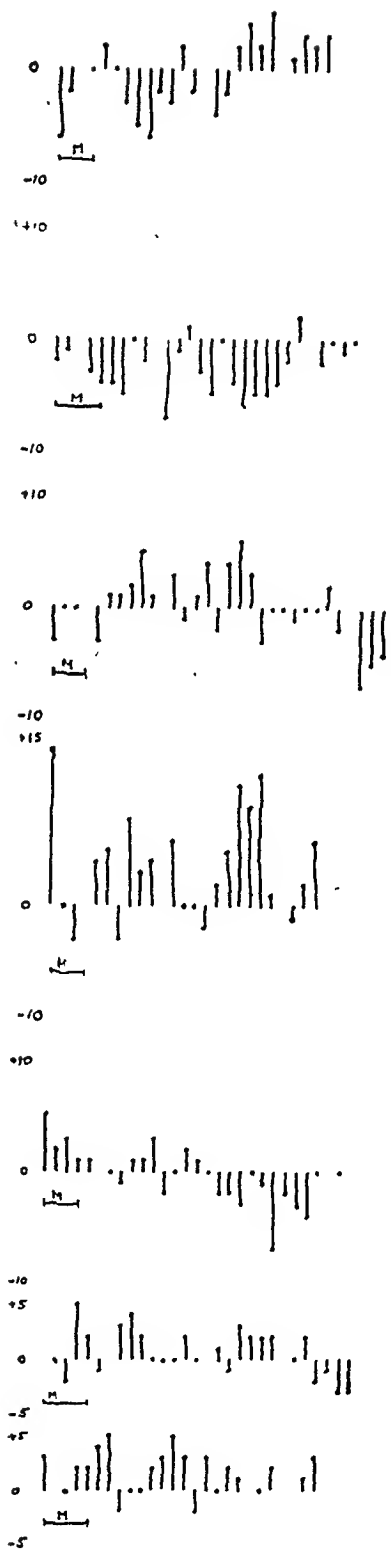


Fig. 1.

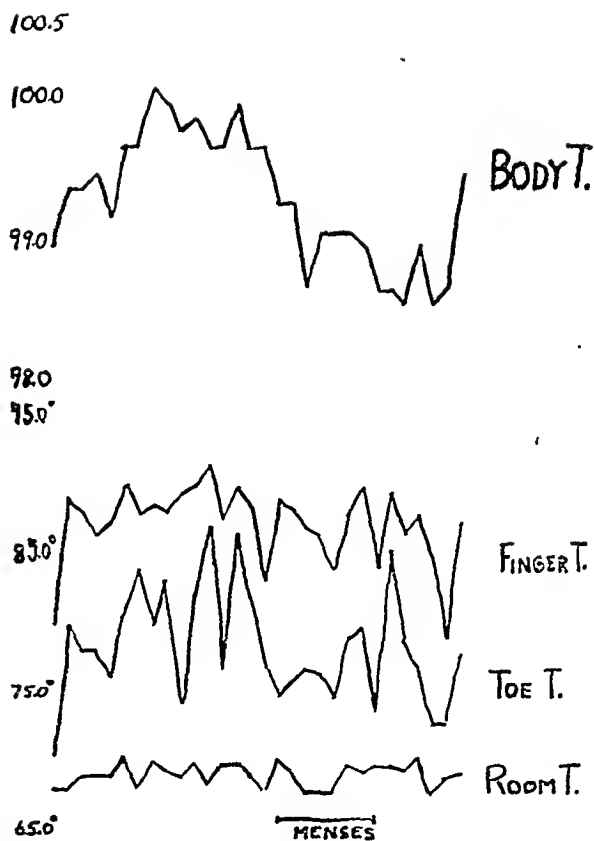


Fig. 2.

Fig. 1.—Index finger P.D. in seven normal menstrual cycles.

Fig. 2.—Temperatures recorded throughout a menstrual cycle. The finger and toe temperatures are arithmetic means of both right and left sides.

mv. The size of the area tested is significant, for areas a centimeter or less apart may demonstrate a P.D. of as much as 20 mv. Potential patterns may be relatively unstable, varying in the same patient from minute to minute with a range of variation exceeding 5 mv. The emotional factors affecting P.D. were not explored but it was noticed that the skin wounds which were painful showed higher P.D. than painless ones. In a single case of a nonulcerated, uninflamed epithelioma of the forehead, no P.D. could be secured between the tumor area and the adjacent normal skin.

Studies in Ovulation

Burr and his co-workers^{4, 12, 13, 14} have reported changes in P.D. between vagina and pubis in the rat and rabbit and between cervix and ankle, cervix and symphysis, and between right and left index fingers in the human being which they believe serve as an index of ovulation. The evidence has been more convincing in lower animals than in human beings. In a single rabbit,¹⁵ they found a gradual rise in P.D. between vagina and pubis with superimposed rapid shifts in P.D. which they believed to indicate ovulation with the rapid rises in P.D. accompanying the physical expulsion of each ovum. Rogers¹⁶ secured correlation between cyclic changes in P.D. and vaginal smears in the rat using vaginal and pubic electrodes. This was confirmed by Nicholas and Carmosino¹⁷ who failed to secure significant P.D. changes in immature or pregnant rats. Burr et al.¹² reported a single observation in a human being wherein a sharp rise in P.D. between vagina and pubis was observed fourteen hours before a punctate hemorrhage of a ruptured follicle was discovered at laparotomy. More indirect evidence was furnished by Langman and Burr¹³ in human cervix to ankle P.D. studies. They found that the cervix was usually 5 to 25 mv. electropositive to the ankle but that, in nine of fourteen cycles studied, it became electronegative for at least one day of the cycle. Barton in Burr's laboratory presented similar type of evidence¹⁴ in a study of P.D. between right and left index fingers, describing peaks significant of ovulation which were absent in men or in women during the menopause. Snodgrass et al.¹⁸ repeated this work but could not find any difference between the types of tracings secured in normal menstruating women and those from surgical castrates or pregnant women. Barton could not correlate index finger P.D. and eyelid body temperatures. She also found that "significant peaks" in index finger P.D.'s occurred in every decile of the menstrual cycle including the menses and that many single cycles showed multiple peaks. Langman and Burr's cervix to ankle P.D. peaks occurred on the 3rd, 6th, 7th, 8th, 13th, 14th, 18th, and 21st days of the cycles.

Using Burr and Barton's index finger technique, wherein the P.D. is measured between the right and left index fingers immersed in beakers of saline connected by saline bridges to the electrodes, six normal nulliparous laboratory workers with regular menstrual cycles were tested daily throughout at least one full cycle. Burr's finding that the pressure of the ball of a finger against the wall of the beaker may modify the P.D. was repeatedly confirmed. This may be attributed to the fact that pressure causes a portion of the digit to lose electrical contact with the saline and the resultant P.D. reflects that of the skin surface still immersed in the fluid. As the dorsum of the finger is electropositive to the volar surface, the P.D. shift on pressure is to the positive side. With a surface area as large as a digit, the resultant P.D. reflects a series-parallel type of relation between multiple areas of widely varying P.D. and the digital P.D. changes may be due to changes in electrical potential of the skin of the entire digit or of only small areas of the digit.

In two patients, the P.D. between mid-vagina and pubis was determined along with the index finger P.D. The midvaginal to pubis potential differences fluctuated widely with multiple peaks and reversals of polarity. Fig. 3 demonstrates such scattering as to call for little correlation between index finger P.D. and vaginal-pubic P.D.

Reboul et al.²⁰ described typical P.D. shifts with vaginopubic leads in the rat when the follicle was artificially ruptured. In several rats, no shift in P.D. between vagina and pubis could be secured on gross trauma to ovary or uterus. With leads so placed, I have been unable to secure any P.D. shift unless one of the electrodes was placed on the traumatized area.

I share the opinion of Snodgrass et al. that digital P.D. study cannot be used as an index of ovulation in the human being. The vaginal-pubic P.D. in the human being, at present, is not capable of interpretation. To explain the more regular findings in lower animals, the statement of Rogers¹⁶ must be considered, "the rise in P.D. comes at the time of sloughing of vaginal epithelium." His studies were in rats whose vaginal mucosa displays enormous morphologic changes within the estrus cycle. It seems doubtful that the relatively minute morphologic changes in the human vaginal mucosa throughout the menstrual cycle will be reflected in P.D. changes which would exceed the errors of instrumentation. It is difficult to understand how ovulation would affect the skin of the digits in a unilateral manner.

Summary

With the Schorr-Lamport millivoltmeter method of registering potential, ovulation could not be determined in the human being.

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Fig. 1 indicates the results secured. The polarity of the fingers changed frequently and there is a wide scatter of "peak" days throughout the cycles. "Peak" potential differences exceeded others by only a millivolt or two which is within the field of experimental error for this apparatus.

Snodgrass et al.¹⁸ interpreted the P.D. changes as primarily due to cutaneous vascular conditions with the resultant local temperature one of the major determining factors. Burr found that by heating portions of the saline bridges, a 1 mv. P.D. change was gained for each 2.5° C. temperature differential. In a single subject, it was found that mechanical obliteration of the arterial circulation caused the temperature of the skin of all the digits to fall at approximately the same rate. With skin thermocouples applied to the middle digits, the P.D. between the index fingers was secured during the period of pulse obliteration. The skin temperature fell 1.3° C. for a 1 mv. P.D. change over a span of 5° C.

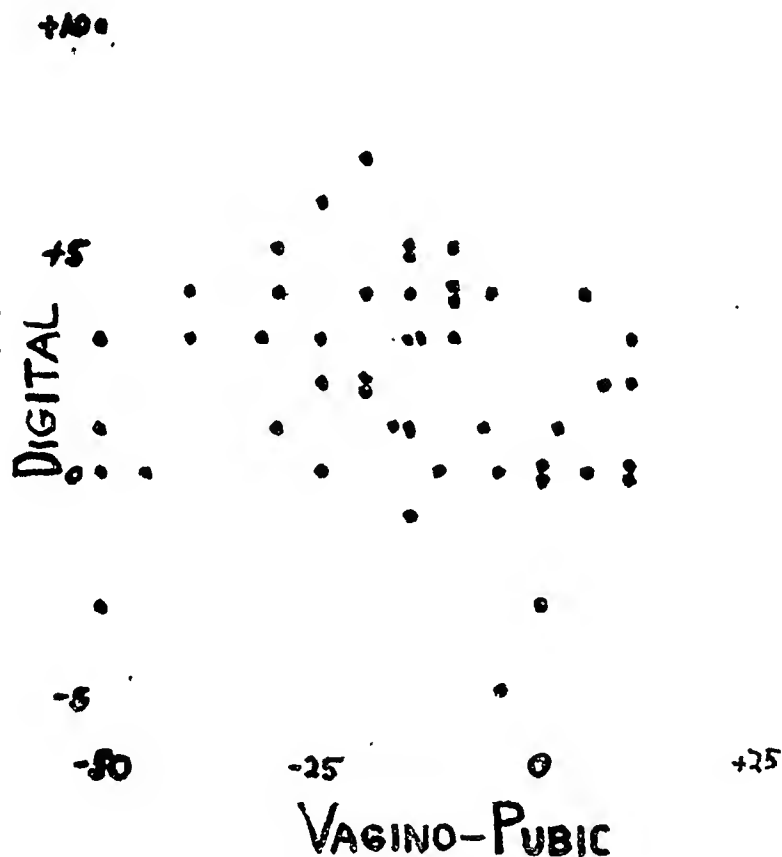


Fig. 3.—Comparison of digital P.D. and vagino-pubic P.D. throughout the menstrual cycle of two patients.

Peculiarly, the P.D. change persisted for twelve minutes after the circulation was restored to normal and the skin temperature returned to the prestriction level. Inasmuch as P.D. is affected by local skin temperature, the skin temperatures of the base of the distal phalanges of both index fingers and great toes and rectal temperatures were taken daily under basal conditions throughout the menstrual cycle of four patients. Fig. 2 presents a typical tracing. Although the finger and toe temperatures fluctuated with the cycle for a span as much as 15° F., the difference between the temperatures of the right and left fingers and toes varied less than 3° F. A difference in skin temperatures cannot therefore be the sole explanation of the observed P.D. changes.

In the 118 cases with pathologic ovaries, the ovarian abnormality was the reason for operation in 54 patients. Sixty-five cases were operated on primarily for leiomyomas, inflammatory disease, and other entities. Even in the fifty-four cases with the important lesion in the ovary, associated gynecologic abnormalities were found in twenty-seven cases, or exactly half.

Table I shows the various ovarian abnormalities in the 118 cases.

TABLE I. OVARIAN ABNORMALITIES (118 CASES)

| | NO. | AGE |
|--|-----|-------|
| Pelvic endometriosis with ovarian involvement | 15 | 18-50 |
| Pseudomucinous cystadenoma, histologically benign | 7 | 42-52 |
| ? early malignancy | 1 | 68 |
| Serous cystadenoma, papillary, histologically benign | 4 | 15-71 |
| Cystic tumors, histology indefinite due to necrosis or infection | 2 | 27-38 |
| Fibromas | 4 | 22-52 |
| Angioma | 1 | 46 |
| Dermoid cysts | 4 | 21-35 |
| Follicular cysts, multiple | | |
| History of abnormal bleeding | 8 | 45 |
| No history of abnormal bleeding | 37 | |
| Lutein cysts | | |
| Cystic corpora lutea, abnormal bleeding | 6 | 34 |
| Cystic corpora lutea, no abnormal bleeding | 14 | |
| Theca lutein cysts, abnormal bleeding | 4 | |
| Theca lutein cysts, no abnormal bleeding | 9 | |
| Hematoma of corpus luteum with intra-peritoneal hemorrhage | 1 | |
| Granulosa cell tumors | 2 | 37-43 |
| Carcinoma—arising in | | |
| pseudomucinous cystadenoma | 3 | 37-68 |
| papillary serous cystadenoma | 1 | |
| Solid carcinoma | 4 | |

TABLE II. ASSOCIATED PATHOLOGIC LESIONS

| | |
|--|----|
| Leiomyomata uteri | 58 |
| Pelvic inflammatory disease | 32 |
| Endometriosis, direct (adenomyosis) | 10 |
| Endometrial abnormality as hyperplasia | 19 |
| Prolapsus uteri, severe | 4 |
| Ectopic pregnancy | 2 |
| Lacerations due to childbirth requiring repair | 3 |
| Cervical polyps | 6 |
| Parovarian cysts | 6 |
| Carcinoma arising (?) in parovarian cyst | 1 |
| Sarcoma arising in broad ligament | 1 |

TABLE III. SYMPTOMS IN 54 CASES WHERE OVARIAN PATHOLOGY WAS PRIMARY REASON FOR OPERATING

| | |
|---------------------------------------|----|
| Nagging pressure or intermittent pain | 48 |
| Acute pain, etc., due to torsion | 5 |
| Increasing dysmenorrhea | 4 |
| Vaginal bleeding | 19 |

TABLE IV. FOLLOW-UP STATISTICS

| | NO. | PER CENT |
|-------------------------------|-----|----------|
| Adequate (over 12 months) | 82 | 69 |
| Partial (less than 12 months) | 22 | 18 |
| No response or lost records | 15 | 12 |

A REVIEW OF OVARIAN PATHOLOGY IN 336 LAPAROTOMIES*

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SO MUCH has been written on the diagnosis and pathology of the rare ovarian tumors, that it seemed timely to try to evaluate again the more usual lesions as seen at operation, and to discuss the old argument of conservation versus removal. It seemed that most authors have not stressed sufficiently the multiple gynecologic lesions often found in the same patient, which may radically affect the approach to treatment. Again, some of the largest tumors in the older patients have proved to be benign, while a smaller tumor in a youngish woman proved malignant.

One thousand eighty-six consecutive gynecologic ward admissions to the Hospital of the Woman's Medical College from Jan. 1, 1942, to Jan. 1, 1947, were reviewed. These admissions included entities such as incomplete abortion, lacerations due to childbirth, and the various neoplasms of the female genital tract, plus or minus inflammatory disease. Three hundred thirty-six laparotomies were performed in this series. Vaginal hysterectomies were not included in that number because it has not been our procedure of choice to remove pathologic ovaries by the vaginal route. In 118 of the 336 laparotomies, both ovaries were conserved; in 120 cases, one ovary was saved; in the remaining 98, both ovaries were removed. Definite ovarian changes considered pathologic were reported by the laboratory in 118 of the 218 specimens in which one or both ovaries were removed. The removal of histologically normal ovaries in 100 laparotomies may be accounted for, in most cases, by fear of insufficient blood supply remaining in cases of pelvic inflammatory disease, large multiple myomas, etc. It has been the Department policy, also, to remove both ovaries when panhysterectomy is done for malignancy, in patients where laparotomy has been necessary at or after the menopause, and in selected cases of pelvic endometriosis.

During this five-year period, 10 patients entered the hospital for pathology in an ovary conserved at a previous operation. Eight of these required re-operation and two are still being observed in the Follow-up Clinic. Six of these ten followed operation for pelvic inflammatory disease, one followed operation for endometriosis of the indirect variety. Of these patients, six had their previous operation in this hospital and four elsewhere. The retained ovary caused symptoms within a period varying from five months to seven years after the first operation.

*Presented at a meeting of the Philadelphia Obstetrical Society, October, 1947.

of 118 cases and none of the four fibromas reported were apparently hormone producing. In cases with multiple gynecologic lesions, the abdominal approach should be used when ovarian pathology is diagnosed. Advanced age should not in itself discourage the surgeon. We have all had the experience that a vigorous elderly person has proved to be a better risk than a delicate younger one. With modern anesthesia, early ambulation, and adequate supportive therapy, one should try to give the patient comfort in her remaining years. The oldest patient in our series was 71 years old and proved to have a benign serous cystadenoma of large size. In the past eighteen months, peritoneal carcinomatosis was seen from a primary ovarian carcinoma in a white girl of fourteen in the Albany Hospital and a Negro girl of 17 years of age at the Philadelphia General Hospital. One of the most discouraging entities with which we have to deal is primary ovarian carcinoma. It should be emphasized again that the presence of one lesion of the genital tract does not protect the patient from others. We should not relax when the discovery of a polyp may explain vaginal bleeding, or a large cystocele and prolapse may explain pelvic pressure. Silence is characteristic of ovarian neoplasms until complications produce symptoms, by which time cure is often not possible. Whether to remove or conserve ovarian tissue is still at times a most difficult decision. The careful training of every resident in gross and microscopic pathology and in the anatomy of ovarian blood supply cannot be overstressed. One must individualize each case of inflammatory disease and endometriosis on gross findings. Some eminent authorities, such as Dr. Arthur Curtis and the late Dr. John Sampson, have questioned the efficacy of retained ovarian fragments in preventing hormonal difficulties in younger women. A high index of suspicion is probably our greatest safeguard and removal of involuting ovaries at laparotomies near or during the menopause should probably be routine.

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Discussion

DR. LEWIS C. SCHEFFEY.—Dr. Pettit's presentation has given occasion for ample discussion of the controversial subject of ovarian conservation.

There is a monument in Rome, Georgia, to an early gynecologist, Robert Battey, whose name is partly remembered for his advocacy, in 1876, of the widespread removal of ovaries for indications ranging from absent uterus with endangered health and absence of menstrual flow to insanity, epilepsy, physical and mental suffering. It was quite the furore of the day. We have come a long way since then. It is not unusual for a young woman, with pain on one side of the pelvis or the other, to give, as a most important point in her history, that of a previous operation for such sort of pain—namely, appendectomy and removal or partial resection of one or both ovaries. Most of these patients have been first operated upon by sev-

TABLE V. CARCINOMA FOLLOW-UP (EIGHT CASES PROVED CARCINOMA)

| | | |
|--|----|---|
| Dead (or presumed dead) | 7 | (palliative operation 6 bilateral carcinoma) (complete operation 1 unilateral carcinoma) |
| Living with metastasis | 1 | (considered operable unilateral carcinoma) |
| Living with no symptoms or signs metastasis | (1 | ? malignant, 7 months postoperative) |

Of the two cases of granulosa-cell tumor, one has disappeared from our clinics. The other has had a pregnancy in the three-year period, has had to date no known recurrence.

The four cases of fibromas, four cases of dermoid cyst were all unilateral tumors.

The fifteen cases of indirect endometriosis were treated in nine patients by unilateral oophorectomy, in six cases by bilateral oophorectomy. Where the disease was sufficiently advanced to warrant bilateral oophorectomy, postoperative deep x-ray therapy was also given. Thirteen of these patients have been discharged from Follow-up Clinic after observation of over one year; two are still being watched. No recurrence of disease has been found as yet.

Comment

It is interesting and important, that the angioma, three fibromas, and two of the dermoid cysts which were found at operation and on section of the ovaries in the laboratory, had not been suspected preoperatively. Dr. Theodore Cianfrani at the University of Pennsylvania recently reported seven unsuspected neoplasms on laboratory examination of 1,500 apparently normal-appearing ovaries. A private case of Dr. F. Marian Williams, operated upon during the time covered by our series, proved on section to have a serous papillary cystadenoma 1 cm. in diameter in an ovary 3.5 by 2.0 by 1.2 cm. A photomicrograph of this tumor will show its rather alarming histology. A typical dermoid cyst as shown was removed with tubovarian masses and adhesions typical of chronic pelvic inflammatory disease. A right ovary had a small white nodule at its proximal end (total ovary 4.2 cm. in length) which proved on microscopic examination to be a small angioma, possibly a lymphangioma. This ovary accompanied a large myomatous uterus to the laboratory. These comments should re-emphasize the importance of careful inspection of ovaries under good light at the time of operation. If the blood supply to the adnexa about to be conserved is adequate, and one is planning to leave it in the patient, biopsy of areas which seemed abnormal to either touch or vision should certainly be advocated.

The fact that associated gynecologic lesions were present in 27 of our cases operated upon primarily for ovarian disease is worthy of further comment. Two of our largest pseudomucinous cystadenomas were in postmenopausal women, aged 58 and 68 respectively, who came to clinic primarily because of second degree prolapsus. A similar private patient, aged 68 years, came to me at this same period for bleeding from a pedunculated cervical fibroid. Further examination revealed a pseudomucinous cystadenoma extending to the umbilicus. None of these three women was complaining of her abdominal tumor, two had histologically benign lesions and one had the small area of metaplastic epithelium shown in the slide. No cases of Meigs' syndrome were encountered in the group

Dr. Pettit mentioned inoperable carcinoma of the ovary. Frequently x-ray renders these patients operable. Since x-ray does not kill the cancer they should have a panhysterectomy and bilateral salpingo-oophorectomy. Some of these patients will survive in spite of extensive involvement.

Dr. Pettit brought up the subject of unsuspected ovarian pathology discovered in normal appearing ovaries that have been removed. One naturally wonders if the ovaries were really normal to inspection and palpation. At Philadelphia General Hospital, the standard treatment for years in pelvic inflammatory disease has been a complete ablation of the pelvic organs. (There is more of an attempt at conservatism today.) In this vast source of material, ovaries were predominantly cystic and neoplastic disease in such instances was not noted.

The best guide a surgeon can have today as to the necessity for oophorectomy is provided in Novak's classification of ovarian tumors. Novak divides the ovarian enlargement into nonneoplastic and neoplastic groups. In the nonneoplastic group he has listed the follicular, lutein, germinal inclusion and endometrial cysts. With the exception of the endometrial growth, surgery is unnecessary in this group.

DR. PETTIT (Closing).—I had hoped my paper would cause some reactions and it did. I think I would like, in view of the discussions, to point out to the audience that I made on my charts the differentiation between the cystic ovaries which were accompanied by abnormal bleeding and those which were not. I did that for the purpose of bringing out points in the discussion which have come up. I think we are agreed, fundamentally, that we wish to be conservative and I think we all are removing fewer cystic ovaries than were taken out formerly. The associated pathology explains some of those cystic ovaries. Those with abnormal function are not always identifiable histologically. We all know that ovarian adhesions are likely to be the site of cyst formation. There were 32 cases of inflammatory disease which cuts down some on our apparent delinquency. In a series of cases taken consecutively with a large number of operators, our statistics are conservative compared with recent reports in the country at large. Concerning surgery in carcinoma of the ovary, by palliative surgery I did not mean that attempts were not made to remove all possible carcinomatous tissue, I meant that ascites and local extension were already present and extensive. I believe as you do, Dr. Beecham, that major surgery should be done on these case if possible. Unfortunately, in this particular group, we were unlucky because x-ray therapy plus surgery did not get these patients into an operable state. It was a fact that they were seen too late.

eral surgeons, but gynecologists are not guiltless either. In the vast majority of such instances unrecognized follicular or corpus luteum cysts have been ignorantly regarded as offending neoplasms, and a vital gound has been sacrificed or damaged.

Now the question in my mind is that, when we are operating to correct pelvic pathology, we should not remove ovaries that appear and feel normal; and the presence of tiny cystic elevations is usually normal. Neither do I see how we can simply draw an arbitrary line at any particular age regarding ovarian removal. What we elect to do depends upon individualization of the patient at hand. In all my experience at Jefferson Hospital, I have only once encountered malignant change in conserved ovaries.

Naturally, in pelvic malignancy, all the pelvic organs should be removed, and perhaps in women of the older age group, conservation of apparently normal ovaries would not be so important. Certainly, however, there are many instances in which ovarian conservation is followed postoperatively by much less vasomotor disturbance than when the ovaries have been removed. Even when technical reasons require ovarian removal, it is possible to use some healthy ovarian tissue by resecting it from the removed ovary and transplanting it beneath the rectus fascia, or even by allowing it to remain in situ in the neighborhood of the infundibulopelvic ligament. These bits of ovarian tissue seem to function well, and such procedures are worth while when ovaries cannot be left in situ as is so often the case when dealing with chronic pelvic inflammatory disease.

It has been mentioned that careful inspection of the ovaries may reveal the possibility of the presence of a true neoplasm, small in size, and, in such instances, I agree that it is good practice to bisect the ovary and resect such a localized tumor. I have done this on several occasions, and twice I have been rewarded by finding, 1, a tiny dermoid, and 2, a luteoma.

I think that every ovary visualized shows a number of cysts, but they are usually retention cysts and are nonneoplastic. One of the points that we constantly impress upon our students is to study the classification of cystic enlargements of the ovary, emphasizing the difference between nonneoplastic cysts of the ovary, which are functional, and true neoplastic cysts, which may be benign or malignant. Practitioners, too, should be well informed in this respect.

DR. CLAYTON T. BEECHAM.—Today we all agree that the female pelvis in general, and the ovary in particular, receive a high degree of surgical assault and abuse. This is not warranted, but the attack continues unabated. Dr. Pettit mentioned 79 cases that were diagnosed as pathologic ovaries and had nothing more than follicular or lutein cysts. I have never seen a normal ovary that did not have normal follicular cysts in it. I sincerely wish the surgeons of Philadelphia and of America would cease to regard the follicular cyst as a surgical entity. I do not see any reason for their removal and cannot agree with their removal because of bleeding. The cause of bleeding is not from follicular cysts but from endocrine imbalance.

Mention has been made of Crossen's advice for removal of normal ovaries at age 43 or more in all women having pelvic laparotomies. A few years ago he had a lower age limit, i.e., 40. One famous gynecologist said years ago that no woman needed her ovaries except a neurotic individual. Then recently, another well-known gynecologist stated that a woman over 35 does not need her ovaries. Such an understanding of ovarian function and female endocrinology is a little hard to understand. Yet, unfortunately, it is in everyday use in this country. I would say, if we are going in for prophylactic surgery against cancer, why take on such an uncommon malignancy. I have not heard Crossen propose bilateral mastectomy for women because they are on an operating table and over 43 years of age. We looked up the last thousand gynecologic admissions to our private service and found unilateral or bilateral oophorectomy for neoplastic disease of the ovary in thirty-four instances. Five of these cases were malignant. From my own figures, I have disregarded Crossen's remarks and believe they have been given too much publicity. Many things have been handed down to us in all branches of medicine and they constitute nothing more than the perpetuation of error.

of this drug for amnesia and analgesia was found to be sufficient for delivery also. When necessary, delivery was completed under ether, gas-oxygen, or local anesthesia. In Group Two a deliberate attempt was made to complete delivery under intravenous sodium vinbarbital alone without any supplemental anesthesia.

The patients in Group One comprised 145 primiparas and 105 multiparas, ranging in age between 18 and 45 years. Presentation and position in this group were 12 breech and 234 vertex (left occipitoanterior 115, right occipitoanterior 107, left occipitoposterior 4, and right occipitoposterior 8).

Method of Administration

The method of administration in this group as a rule was uniform. Demerol (meperidine) and scopolamine were administered when active labor was in progress with uterine contractions four to five minutes apart, or when the cervix showed at least two fingerbreadths dilatation. The initial dosage was $1\frac{1}{2}$ grains of Demerol and $\frac{1}{100}$ grain of scopolamine; $\frac{1}{200}$ grain of scopolamine was given one-half hour later. Either Demerol or scopolamine or both were repeated as indicated as labor progressed. Sodium vinbarbital was administered intravenously when the cervix was fully dilated in both primiparas and multiparas, and was repeated as necessary if restlessness with pains occurred at any time prior to the completion of labor. Occasional restlessness due to the administration of Demerol and scopolamine was controlled by the intravenous administration of sodium vinbarbital before full dilatation had occurred.

Forty-three patients in Group One, or 17.2 per cent, received no preliminary medication, as they entered the hospital well advanced in labor and ready for intravenous sodium vinbarbital. These 43 patients were "screaming" multiparas; sodium vinbarbital is an excellent drug for this group, since the patient is asleep in the course of two minutes and is well under control for proper preparation and delivery.

At the beginning of this study sodium vinbarbital was injected intravenously in an initial dose of 4 or 5 grains, but as our experience with this drug became more extensive the dosage was increased so that it is now routine practice to give an initial dose of 10 grains followed by 5 or 10 grain doses as indicated until completion of labor. It is at this point that failures will occur with the intravenous use of this barbiturate if an insufficient dosage is employed. Before full acquaintance with the drug is achieved there is a tendency to hesitate to give the full 10 grain dose intravenously, since the patient may appear to be well sedated and asleep after 5 or 6 grains have been injected.

In the present study an attempt was made to individualize dosage (Table I). However, this has been found to be unnecessary and, in fact, it is less advantageous to individualize the initial dose. A routine initial dose of 10 grains, irrespective of the body weight of the patient, has been found to be the most satisfactory method. Subsequent dosage then is individualized and regulated by the response of the patient, as gauged by restlessness with pain. The ideal reaction to uterine contractions while under this drug manifests itself simply in increased respiration with a snoring sound, but with no movements except a bearing down effort. When the patient exhibits a desire to roll over or move her arms and legs in a restless manner with pains, it is an indication for further medication then or relatively soon. This has been observed to be the best criterion for further medication in this group and is without danger.

The length of labor before any medication was given varied from one hour to seventeen and one-half hours. The elapsed time between preliminary medica-

THE CLINICAL USE OF SODIUM VINBARBITAL BY THE INTRAVENOUS ROUTE IN OBSTETRICS*

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SODIUM vinbarbital† is a soluble barbiturate provided in capsules for oral administration and in sterile solution for intravenous use. It is classed as a sedative, hypnotic, and analgesic agent. This drug has a wide margin of safety. Its action is of short duration and it is relatively free of undesirable side-effects such as excitation or "hang-over."

The pharmacology and toxicology of this barbiturate have been investigated by a number of workers,¹⁻⁴ particularly with respect to its effect on blood pressure and respiration, and it appears that sodium vinbarbital is a relatively nontoxic compound when employed in therapeutic doses. It has the advantages of rapid action and low toxicity, and causes no depression of the respiratory or cardiac centers. The drug is largely detoxified in the liver.

Many hospitals, including ours, have not the resident staff that is almost a necessity for the proper administration and guidance of the more complicated routines in labor for the relief of pain and mental stress. Favorable reports on the oral and intravenous usage of Vinbarbital sodium by Prince, Evans, Bernstein, and Lewis brought us to the study and usage of Vinbarbital sodium intravenously at St. Joseph's Hospital. If this method combined a wide margin of safety for both the mother and baby with satisfactory amnesia, analgesia, and anesthetic effects combined with utter simplicity of administration, we felt we would have a drug and method highly advantageous to our needs.

With these factors in mind a study of the intravenous administration of sodium vinbarbital during labor was undertaken. The material presented represents 500 unselected patients from the private service at St. Joseph's Hospital. Since our only past experience with intravenous barbiturate derivatives had been with drugs such as pentothal, precautions were observed with respect to dosage at the beginning of this study until the results to be anticipated with this particular preparation could be ascertained. The dosage then was gradually increased until the present satisfactory dosage levels were established.

The cases reported here have been divided into two groups of 250 patients each. In Group One no attempt was made to deliver under intravenous sodium vinbarbital anesthesia alone, except in those instances in which routine usage

*Presented before the Central New York Association of Obstetricians and Gynecologists, Syracuse, N. Y., Sept. 30, 1947, and the Obstetrical and Gynecological division of the Rochester Academy of Medicine, Rochester, N. Y., Dec. 16, 1947.

†Sodium vinbarbital is the nonproprietary name for sodium 5-ethyl-5- (1-methyl-1-butenyl) barbiturate, and is distributed under the name of Delvinol sodium vinbarbital. The material used in this study was provided through the courtesy of the Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pennsylvania.

dents. No special knowledge or skill was required except the ability to insert a needle in a vein. Any available vein in the upper or lower extremities was used. A 10 c.c. syringe with a 20-gauge needle was employed, and approximately one and one-half minutes were allowed for the injection of 10 c.c. of solution containing one grain of sodium vinbarbital per cubic centimeter. The rapidity and ease of action are remarkable; deep sleep accompanied by deep, regular breathing with good color occurred in the majority of patients before the injection was completed. Restlessness can be avoided entirely by adequate dosage. Additional intravenous sodium vinbarbital medication is given when restlessness with pains is observed, and there has been no evidence in any instance of overdosage with the use of this method.

There was no apparent effect on the duration of labor. Uterine contractions were not diminished in intensity or in rate. Dilatation progressed rapidly, and a large percentage of patients showed a good bearing down action.

Effect on the Mother

Sedation was classified as complete, incomplete, or failure. Complete sedation was obtained in 132 primiparas and 94 multiparas, a total of 226 patients (90.4 per cent). In the restless group of 14 primiparas and 7 multiparas, a total of 21 patients (8.4 per cent) in whom sedation was incomplete, full amnesia was obtained but the patients were restless with pains and difficult to control. Three multiparas (1.2 per cent) were classified as failures with respect to sedation. These patients were drowsy but did not go to sleep, and remembered scattered incidents after therapy. With our present knowledge it is believed that a larger initial dose of sodium vinbarbital or more adequate supplemental administration of the drug would have controlled the restless patients and those in whom sedation was not obtained. Twenty of the group of 24 patients in whom sedation was classified as incomplete or failure were among the first studied and these patients received an inadequate initial dose of sodium vinbarbital. In the remaining four patients the initial dose of 10 grains was satisfactory, but a supplementary dose was not given or was inadequate. There have been no restless cases or failures among the last 175 cases studied in this group of 250.

Additional anesthesia for delivery or repair was not required in 66 primiparas and 55 multiparas, a total of 121 patients (48.4 per cent) beyond the routine intravenous administration of sodium vinbarbital, although no attempt was made in this group to deliver with the use of this drug alone. A small amount of inhalation anesthesia was needed for delivery but none for repair in 44 primiparas and 32 multiparas, a total of 76 patients (30.4 per cent). Either regular inhalation anesthesia or local anesthesia was employed in the remaining 35 primiparas and 18 multiparas, a total of 53 patients (21.2 per cent) for delivery and repair.

In other words, nearly 50 per cent of this group obtained anesthesia effect sufficient for delivery and repair, although this was not deliberately attempted in this group. Another 30 per cent were repaired without further anesthesia. Only 21 per cent required full anesthesia.

The maternal blood pressure was checked before the intravenous administration of sodium vinbarbital and every twenty to thirty minutes thereafter until delivery. There was no change in blood pressure of any significance except in four cases, and these were not alarming changes. In one of these patients there was a slight rise in blood pressure, and in the remaining three a slight drop. These minor changes were transitory and of short duration.

Respiration was not affected in any case. Respirations remained full, regular, and at the rate of 18 to 20 per minute. Occasionally, because of com-

tion and intravenous sodium vinbarbital ranged from ten minutes to thirteen and one-half hours. In the primiparous group 56 per cent received Demerol and scopolamine over two hours before intravenous sodium vinbarbital therapy and 35 per cent less than two hours before the latter. In the multiparous group 20 per cent were given Demerol and scopolamine two hours or more before the barbiturate and 80 per cent under two hours.

TABLE I. DOSAGE OF SODIUM VINBARBITAL

| NO. OF PATIENTS | PERCENTAGE OF TOTAL PATIENTS | TOTAL DOSAGE* |
|-----------------|------------------------------|---------------|
| 3 | 1.2% | 20 grains |
| 1 | 0.4% | 16 grains |
| 20 | 8.0% | 15 grains |
| 4 | 1.6% | 13 grains |
| 5 | 2.0% | 12 grains |
| 147 | 58.8% | 10 grains |
| 67 | 26.8% | 8 grains |
| 2 | 0.8% | 7 grains |
| 1 | 0.4% | 6 grains |

*In this group 215 patients were given a single intravenous dose of sodium vinbarbital and 35 patients received 2 or more doses.

The period between intravenous sodium vinbarbital administration and delivery varied from five minutes to eleven hours. Delivery occurred in 70.8 per cent of the primiparas under two hours and in 29.2 per cent over two hours. In the multiparous group 93.2 per cent delivered under two hours, and 6.8 per cent over two hours. These results tend to corroborate the impression that uterine contractions were not diminished or delayed by the use of this drug and labor was not prolonged. In fact, in many instances labor progressed much more rapidly after administration of intravenous sodium vinbarbital. The response to rectal or perineal pressure with bearing down effort was good under this therapy.

The elapsed time between the onset of labor and the intravenous administration of sodium vinbarbital, the elapsed time between preliminary medication and sodium vinbarbital intravenously, or the elapsed time between administration of the barbiturate and delivery did not in any way affect the progress of labor or the reaction of the mother or baby. This is an important point, since sodium vinbarbital can be given intravenously at any time without fear of harm to mother or infant because of poor timing or an inadequate time interval.

The data presented in Table II show that over 70 per cent of patients received intravenous sodium vinbarbital therapy at full dilatation. This routine was adopted for the sake of uniformity in this study and also because the majority of patients were comfortable to this point with preliminary medication. However, the drug can be administered at any stage of dilatation with satisfactory results.

TABLE II. INTRAVENOUS SODIUM VINBARBITAL MEDICATION WITH RELATION TO DILATATION

| PRIMIPARAS | MULTIPARAS | PERCENTAGE OF PATIENTS | FINGERBREADTHS DILATATION |
|------------|------------|------------------------|---------------------------|
| 121 | 63 | 73.6% | Full |
| 11 | 7 | 7.2% | 4½ |
| 9 | 23 | 12.8% | 4 |
| 4 | 10 | 5.6% | 3 |
| 0 | 2 | 0.8% | 2½ |
| 145 | 105 | | |

The intravenous medication in this series was given by the author, by the various interns in the hospital, the graduate nurses on duty, and medical stu-

TABLE III. FETAL MORTALITY (GROUP ONE)

| | | |
|---|----|------|
| Total number of babies delivered | | 256 |
| Stillbirths | 6 | |
| 1 true knot | | |
| 1 abruptio placentae at 7 months | | |
| 1 twin with velamentous insertion of the cord | | |
| 1 monstrosity | | |
| 1 7½ month erythroblastotic infant | | |
| 1 anomaly of umbilical cord | | |
| Neonatal deaths | 5 | |
| 2 6 month twins, lived 1 and 2 days | | |
| 2 6½ month twins, lived 6 days | | |
| 1 congenital atelectasis | | |
| Total number of infants lost | 11 | |
| Gross fetal mortality | | 4.3% |
| Corrected fetal mortality (5 neonatal deaths) | | 2.0% |

TABLE IV. EFFECT OF MEDICATION ON 250 LIVING INFANTS

| DEGREE OF ASPHYXIA | NUMBER OF INFANTS | PERCENTAGE OF INFANTS |
|--------------------|-------------------|-----------------------|
| None | 200 | 80.0% |
| Mild | 31 | 12.4% |
| Moderate | 19 | 7.6% |
| | 250 | |

Method of Administration

The routine for intravenous administration of sodium vinbarbital in this group was identical with that of the previous group of patients, except that at the time of delivery additional sodium vinbarbital was given if sedation was not sufficient for delivery. A total dosage of from 10 to 25 grains (average 15 grains) of sodium vinbarbital was administered intravenously (only one patient received the maximum total dosage of 25 grains). Ten grains of the barbiturate were given routinely as the initial dose at full dilatation, and medication was repeated in 5 to 10 grain doses as necessary.

This group contained 129 primiparas and 121 multiparas. There was 236 cephalic presentations and 14 breech. One hundred six were right occipitoanterior; 111 were left occipitoanterior; 6 were left occipitoposterior; and 13 were right occipitoposterior.

Spontaneous delivery showed 37 primiparas and 50 multiparas. Low forceps showed 93 primiparas and 61 multiparas. Midforceps were used in four primiparas and one multipara. High midforceps were used in two primiparas.

Rotation of the posterior head was done in ten cases, two cases by manual rotation and eight cases by the use of forceps.

One hundred sixty-seven cases had episiotomy and repair performed.

One case of Dührssens incisions of the cervix and one case of Piper forceps in the aftercoming head.

Effect on the Mother

Satisfactory amnesia and anesthesia were obtained with the intravenous use of sodium vinbarbital and no supplemental anesthesia with other agents was required in 246 of these patients (98.2 per cent). Two patients who received a total dosage of 15 and 20 grains of the barbiturate, respectively, were too restless for delivery, and anesthesia was completed with ether. One patient was given ether to control delivery of the head because of a previous rectovaginal fistula. In a fourth patient version was contemplated and ether was given

plete relaxation, the tongue fell against the roof of the mouth impending the air passages. When this occurred, the usual metal airway was inserted.

The only significant pulse changes noted were in nine cases. The change was a slowing of the pulse rate with no alteration in character otherwise or no change in heart sounds or rhythm. This change was of short duration with a return to the original rate. This effect is sometimes noted with Demerol alone.

Every woman in this series was questioned as to her memory of labor and delivery. In 99 per cent there was complete loss of any recollection of events from the intravenous administration of sodium vinbarbital until some hours after delivery. All patients slept from one to six or eight hours following delivery. Sleep was quiet, deep, and restful; on awakening the patients felt refreshed and there were no complaints of "hang-over." No restless patients were encountered in this post delivery period. There was no instance of nausea or vomiting and no apparent contraindication to the intravenous use of sodium vinbarbital. All patients were satisfied with their experience and expressed a desire for this type of medication in the future.

Effect on Infants

The data on fetal mortality are presented in Table III. Of the six still-born infants, four died prior to admission of the mother to the hospital. These were the monstrosity, the erythroblastotic infant, and eight-month twin with velamentous insertion of the cord, and the complete abruptio placentae at seven months. These four deaths can in no way be attributed to the use of sodium vinbarbital. Two infants died during labor, one had a true knot of the cord, and the second one, a ruptured umbilical cord vessel from an anomaly of the cord. These deaths likewise were not attributable to the intravenous barbiturate therapy. Medication also was not a factor in the four neonatal deaths of premature twins. The neonatal death due to congenital atelectasis cannot be definitely proved one way or the other to have been affected by the barbiturate, since an autopsy was not permitted. However, the impression was obtained that this death was not influenced by medication. The infant breathed and cried spontaneously and immediately, but the breathing was obstructive in type, and true thoracic breathing was never established. It is believed that this baby might have been saved by bronchoscopy.

A change in the fetal heartbeat was noted in only four instances in this series, and was characterized by an increase from 140 to 160 or 170 for a short period. All four of these babies survived.

Considerable care was exercised in collecting data with respect to the effects of medication on the infant. Those infants who cried spontaneously were not considered to have any asphyxia. Infants who needed only the clearing of the air passages were classified as mildly asphyxiated. Infants who in addition required carbon dioxide and oxygen were considered to be moderately asphyxiated. No respiratory stimulant other than carbon dioxide and oxygen was required in any infant. The color of all the babies was good, and no great difficulty was encountered in establishing respiration in any group. A further breakdown of the 19 babies classified as moderately asphyxiated (Table IV) revealed that in 13 of these other factors were involved, such as a long hard labor, partial separation of the placenta, midforceps delivery, or version complicating the picture and contributing to fetal embarrassment. The elapsed time between administration of sodium vinbarbital and delivery or the size of barbiturate dosage did not appear to play any part in the incidence of asphyxia in this series.

Group Two comprised 250 patients in whom a deliberate attempt was made to deliver under intravenous sodium vinbarbital alone without supplemental anesthesia.

refreshed. Restlessness was not a common feature. When it occurred, further intravenous administration of sodium vinbarbital effectively controlled it.

5. General anesthesia when indicated was not complicated by the previous use of sodium vinbarbital.

6. Uterine contractions were unaffected by the use of this barbiturate. Labor was not prolonged, and postpartum hemorrhage did not occur in this series.

7. It is recommended that an initial dose of 10 grains (0.6 Gm.) be administered routinely. Subsequent doses of 5 or 10 grains (0.3 or 0.6 Gm.) then are given when restlessness is evident with uterine contractions.

8. The results indicate that sodium vinbarbital, administered intravenously, is a very satisfactory drug for the induction of obstetric amnesia, analgesia, and anesthesia.

Note.—An additional 500 patients have been delivered, since this paper was submitted, with comparable results.

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to relax the uterus completely. Thus there were actually only 2 failures, not with respect to analgesia and amnesia but with regard to full anesthesia, and the percentage of patients obtaining complete sedation then was 99.1 per cent.

Effect on Infants

A total of 252 babies were born to these 250 mothers. No difference from the previous group was observed with respect to the necessity for resuscitation of infants. The administration of sodium vinbarbital for delivery did not increase the incidence of either mild or moderate asphyxia in this group. The data on fetal mortality are given in Table V.

TABLE V. FETAL MORTALITY (GROUP TWO)

| | | |
|---|---|-------|
| Total number of babies delivered | | 252 |
| Stillbirths | 3 | 1.19% |
| (1) contracted pelvis, long labor, late cesarean with death of fetus during operation | | |
| (2) macerated fetuses, dead before admission of mother to hospital | | |
| Neonatal deaths (all premature) | 6 | 2.38% |
| 1 7-month infant, 2½ lb., lived 2 days | | |
| 1 7-month infant, 2 lb. 4 oz., lived 24 hrs. | | |
| 1 5-month infant, lived few hours | | |
| 2 5½-month twins, lived 2 hours | | |
| 1 8-month toxic infant, lived 5 days | | |
| Total number of infants lost | 9 | |
| Gross fetal mortality | | 3.57% |
| Corrected fetal mortality (6 neonatal deaths) | | 1.19% |

Two macerated fetuses dead before admittance to the hospital cannot be attributed to medication. The third stillbirth was distinctly a case that should have been sectioned earlier, and fetal death occurred during cesarean section. This case undoubtedly died because of cerebral damage. In the neonatal group three babies were nonviable infants of five and one-half months. Three babies were six and one-half to seven months prematures weighing less than 3 pounds and toxic. All these babies lived long enough to excuse the barbiturate of complicity, I believe. It will be noted that the increased dosage and of necessity late final dosage for delivery did not alter the fetal mortality rate in this group over the previous group.

There was no maternal mortality in these 500 cases.

Summary and Conclusions

1. In the study presented herein, 500 patients received sodium vinbarbital intravenously for obstetric amnesia, analgesia, and anesthesia.

2. A total of 508 infants was delivered with a gross fetal mortality of 3.9 per cent and a corrected fetal mortality of 1.3 per cent. No fetal death could be attributed to the use of this drug. There was no maternal mortality.

3. Complete amnesia and analgesia were obtained in 497 patients (99.4 per cent). Anesthesia was satisfactory for delivery in 246 patients (98.4 per cent) in whom this effect was attempted.

4. The intravenous administration of sodium vinbarbital is a simple procedure, requiring no special skill. Induction of sleep was almost instantaneous; there were no "hang-over" symptoms, patients awakening rested and

going to be necessary, the rate of increase was more rapid. The vaginal smears were repeated until full estrogen effect was observed or until the symptoms had reached their minimum level.

The vaginal smears were stained with Shorr's¹² stain. The patients were classified into four groups depending on the severity of their symptoms. A similar classification has been used by Fluhmann.⁷ The vaginal smears were graded as Reaction 1, 2, 3, or 4, as described by Geist and Salmon.⁸ Reaction 1 represented complete estrogen deficiency and was characterized by a predominance of basal cells with leucocytes, erythrocytes, and debris. Reaction 4 represented full estrogen effect with large flat cells with pyknotic nuclei, leucopenia, and no debris. Reactions 2 and 3 are intermediates between these two extremes.

Results

GROUP I—13 PATIENTS

RELIEF OF SYMPTOMS:

Partial 1

Satisfactory 12

MINIMAL EFFECTIVE DOSE

NO. OF PATIENTS

0.2 mg. per day

1

0.3 mg. per day

2

0.4 mg. per day

3

0.5 mg. per day

3

1.0 mg. per day

3

1.5 mg. per day

1

GROUP II—7 PATIENTS

RELIEF OF SYMPTOMS:

Partial 2

Satisfactory 5

MINIMAL EFFECTIVE DOSE

NO. OF PATIENTS

0.2 mg. per day

1

0.3 mg. per day

2

0.4 mg. per day

3

1.0 mg. per day

1

GROUP III—4 PATIENTS

RELIEF OF SYMPTOMS:

Partial 0

Satisfactory 4

MINIMAL EFFECTIVE DOSE

NO. OF PATIENTS

0.4 mg. per day

1

0.5 mg. per day

2

1.5 mg. per day

1

GROUP IV—7 PATIENTS

RELIEF OF SYMPTOMS:

Partial 2

Satisfactory 5

MINIMAL EFFECTIVE DOSE

NO. OF PATIENTS

0.5 mg. per day

1

1.0 mg. per day

2

1.5 mg. per day

2

2.0 mg. per day

2

A CLINICAL EVALUATION OF DIENESTROL IN THE CLIMACTERIC

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DIHYDROXI-DIPHENYL-HEXADIENE, commercially known as dienes-
trol,* was first discovered to have estrogenic activity by Dodds and his
associates in 1938.³ At this time, the work done with the drug was restricted
to animal experiments. These investigators determined, using castrate female
mice, that 100 per cent estrus could be produced with a dosage of 3 gammas of
dienestrol by mouth, while with diethylstilbestrol only 70 per cent estrus was
obtained. Emmens⁴ determined in similar experiments that dienes-
trol by mouth produced results comparable to four times the amount of diethylstilbestrol. Due
to the difficulty and the expense of synthesis of the drug, no further investigation
was carried out at that time.

Recently the development of an easier and cheaper method of synthesis has
resulted in further investigation of its clinical properties. In 1938, Barnes^{1, 2}
investigated a group of menopausal patients, and determined that a dosage of
0.1 mg. twice daily was sufficient to relieve menopausal symptoms. Senile
vaginitis and concurrent symptoms were relieved in several cases. None of these
patients exhibited any symptoms of intolerance.

Finkler and Becker,^{5, 6} in 1946, in a series of seventy-three patients in the
climacteric, determined that there was a high incidence of relief of symptoms and
a very low incidence of toxicity on dosages of 0.2 to 1.5 mg. per day.

Sikkema and Severinghaus,¹³ also in 1947, in a series of twenty-one patients,
reported similar findings and suggested optimum dosages of 0.1 to 0.6 mg. per
day. There were no toxic effects.

Rakoff, Paschkis, and Cantarow,¹¹ using the drug in forty menopausal
women, determined the dosage range from 0.1 to 1.0 mg. per day with no symp-
toms of intolerance.

Method of the Present Study

A clinic was established for menopausal patients at Firmin Desloge Hospital
in St. Louis, and all patients who complained of symptoms which might be due
to the climacteric were referred for evaluation and treatment. The patient, on
her initial interview, was questioned and an evaluation was made. Those patients
who seemed to have predominating psychic factors were eliminated from the
study. Those patients with organic disease whose symptoms might simulate
those of the climacteric were also eliminated.

The patients who were chosen for the study were examined gynecologically
and a vaginal smear was made. They were started on dienes-
trol at a dosage of 0.1 mg. per day. The patients were seen weekly and questioned as to symp-
toms. Each week the dosage was increased until symptoms reached a constant
minimum level. Each week a vaginal smear was taken. The dosage increase
was usually by 0.1 mg. per day each time the patient was seen. In a few
patients, in whom it was obvious after a short time that larger doses were

*Dienestrol was supplied by White Laboratories, Inc.

3. Dienestrol produces an unusually low number of toxic effects and, as far as this study is concerned, none that were not easily controlled.

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Summary and Discussion

Fifty-nine patients were treated in the clinic. Of these, thirty-one are reported. The remaining twenty-eight were eliminated because of irregular attendance and failure to use the medication as prescribed. Of the reported group, four were premenopausal, sixteen had experienced a spontaneous menopause, and eleven had experienced a surgical menopause. Of the reported group, 84 per cent were satisfied with the relief provided by dienestrol. The remaining 16 per cent admitted partial relief but not complete satisfaction.

From the above tabulations, it can be seen that, as the severity of symptoms increases, the dosage necessary for maximum relief increases. This, of course, is not true in all cases, but there is a definite trend in that direction. The dosage range is from 0.2 mg. per day to 2.0 mg. per day. The majority fall into a range of 0.4 mg. per day to 1.5 mg. per day. An occasional patient requires more or less. Nineteen of the thirty-one were maintained with satisfaction on 0.5 mg. per day or less, six more between 0.5 mg. per day to 1.0 mg. per day and seven needed 1.0 mg. per day to 2.0 mg. per day. Because of the discrepancy between these doses and those previously reported, attempts were made to decrease the dosage in those patients who were taking 1.5 to 2.0 mg. per day. Invariably these attempts resulted in recurrence of symptoms.

Thirty of the thirty-one patients exhibited full estrogen effect in their vaginal smears, which, in almost all cases, occurred together with or soon after maximum relief of symptoms.

Of the total group, one patient experienced nausea and vomiting on a dosage of 0.5 mg. per day. The drug was discontinued for one week and restarted at the level of 0.3 mg. per day with no further evidence of toxicity. Of the total group, two patients exhibited withdrawal bleeding. One of these was a twenty-seven-year-old castrate who had on several occasions received estrogen therapy of various types. Several times during these courses of treatment she bled severely. Twice the bleeding was so profuse that a dilatation and curettage were deemed necessary. After stabilization on dienestrol at the level of 2.0 mg. per day, she was placed on intermittent courses of treatment of twenty days with a ten-day interval. During each ten-day interval, she experienced withdrawal bleeding which simulated a normal menstrual period. The other patient who bled was sixty-three years old, twenty years postmenopausal. This patient voluntarily stopped taking medication for a period of one week. During this period she spotted for one day.

Of the total group, there was no patient who felt that dienestrol was totally ineffective.

Conclusions

1. Dienestrol is an active estrogenic substance. It is efficient in the treatment of the symptoms of the climacteric and produces vaginal changes characteristic of any estrogenic substance.

2. The optimum dosage of dienestrol varies with the individual. Dosages of 0.2 to 2.0 mg. per day were given during the course of this study. Speaking generally, the dosage of dienestrol parallels the severity of the symptoms.

of the second month, so that the fault was not ascertained. In the repeat sections, where a previous sterilization was supposedly carried out in other clinics and failed, and this was true in six cases, we found the round ligament had been identified as the tube in three cases, and, in two others, the tube had been apparently so buried in adhesions that its structure had not been identified sufficiently for obliteration. In the sixth case, bilateral salpingectomy had been performed by an excellent gynecologic surgeon. At section, the right ovary was found directly adherent over the uterine cornu. We feel that every woman should be offered sterilization at the repeat section if she has one child living and well and the child at current section is apparently healthy and normal. This may appear too conservative but it seems reasonable, that, with the possible difficulties that may arise, it is hardly fair to ask a mother to assume any further risk voluntarily.

| CAUSES FOR SECTION | NO. | PER CENT |
|-----------------------------|-----|----------|
| Placenta previa | 52 | 10.1 |
| Separated placenta | 24 | 4.7 |
| Previous section | 121 | 23.7 |
| Cephalopelvic disproportion | 112 | 21.1 |
| Contracted pelvis | 77 | 15.1 |
| Breech | 5 | .98 |
| Prolapse of cord | 3 | .39 |
| Elderly primipara | 5 | .98 |
| Rheumatic heart disease | 45 | 8.8 |
| Multiple sclerosis | 2 | .39 |
| Pernicious anemia | 1 | .19 |
| Psychosis | 3 | .59 |
| Diabetics | 16 | 3.1 |
| Chronic nephritics | 8 | 1.6 |
| Pulmonary tuberculosis | 18 | 3.5 |
| Fibroids | 5 | .98 |
| Rupture | 3 | .59 |
| Gynecologic operations | 10 | 1.9 |

STERILIZATION

| | |
|------------------------|-----|
| Multiparity | 118 |
| Heart conditions | 33 |
| Tuberculosis | 18 |
| Psychosis | 3 |
| Nephritics | 8 |
| Gynecologic operations | 10 |
| Diabetics | 14 |

Anesthetics.—We are inclined to use nitrous-oxide-oxygen-ether sequence because it definitely contributes to the speed and ease of operation and to the more satisfactory postoperative recovery. To be sure, an anesthetic must be selected for the particular patient, but it goes without saying that no patient's life should be in jeopardy by reason of an anesthetic agent per se. The patient's need is to be evaluated and the anesthetic selected on that basis. The novelty of the anesthesia or the ease of the operating surgeon is decidedly a minor point, the safety of the patient is always the primary consideration.

| | |
|--------------------------|-----|
| N ₂ O-O-Ether | 402 |
| Spinal | 9 |
| Open Ether | 61 |
| Local | 14 |
| Vinethene | 2 |
| Pentothal | 5 |
| Avertin | 7 |

REPORT ON 510 CASES OF CLASSICAL CESAREAN SECTION*

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WE ARE presenting this report of sections from a controlled clinic in which the patients are closely watched and decisions made, for the most part, well in advance of section. The operations were largely performed by the author and his associates, Drs. Loughrey, Ingram, and Huff, trained in and confining their work to obstetrics only. No long trials of labor have been permitted because we believe the competent obstetrician should be able, with the aids at hand, to make a decision without long delay. All patients in whom section is considered are x-rayed and receive the necessary pelvimetry. I favor stereoscopic pictures and want as much detail as possible, so that abnormalities of the infant as well as pelvic incompatibility might be discovered. The classical method has been chosen because of the speed and ease with which the operation is carried to conclusion.

Incidence.—The 510 cases presented are from a total of 21,759 deliveries, or an incidence of 2.3 per cent. The maternal deaths, and these will be discussed more fully later, were six, or a mortality of 1.1 per cent. Of the infants, where live babies were anticipated, twelve died while the mother was resident in the hospital. There were 11 stillborn infants, all diagnosed before operation. The death rate, therefore, is 2.4 per cent. The weights of the children varied from 5 pounds, 1 ounce, to 12 pounds, 9 ounces.

The age incidence ranged from 13 to 47. Curiously, in the youngest of the patients the pelvic disproportion was at its worst. The condition, in one patient, was accompanied by congenital dislocation of both hips, in another, by severe bone tuberculosis, and, in the third patient, by congenital heart disease. We have always been skeptical of accepting congenital heart disease as a legitimate reason for cesarean section, particularly if the patient had grown to adult life with no sign of cardiac difficulty, but, after seeing such an apparently well patient suddenly develop a decompensation, a revision of opinion became necessary. In two patients, both primiparas, one at 44 and one at 47 years of age, with pelvic measurements on the borderline and x-ray showing well-calcified fetuses, section was performed, despite the feeling that, had the patients been younger, tests of labor might have been tolerated. By far the greater number of sections, as would be expected were in the 20 to 30 year bracket.

Some of the sections reported in the list were performed with sterilization at the request of various medical specialists and not primarily as an obstetric problem.

Sterilization.—We sterilize by removing approximately an inch of each tube, obliterating at the cornu of the uterus with continuous catgut on an intestinal needle and folding the distal end of the tube under the broad ligament. While never assuring the patient of a positive sterilization, only one patient has ever reported a pregnancy and, unfortunately, she miscarried at the end

*Presented at the regular meeting of the Obstetrical and Gynecological Society of Pittsburgh on Feb. 2, 1948.

There was a total of five deaths out of 510 or a percentage of 0.98 per cent. These were all before the use of the sulfonamides or penicillin.

Transfusion.—All placenta previa and all separated placenta patients were transfused. If the patient was not in good condition, the transfusion would be given before operation and repeated when necessary. When in doubt, we feel transfusion is good judgment. Unless hematocrit and specific gravity readings are easily available, one is never able to evaluate the loss of blood or the effect of operation combined with the previous loss of blood. Transfusion is of value, using blood pressure and pulse as a check on the amount used. In transfusion, of course, it goes without comment that the blood pictures must be compatible and that careful cross agglutination should be employed.

Ruptures.—Three patients had gone into labor and during the time of getting to the operating room the old scar had ruptured. At operation, three other cases showed a beginning rupture through the old scar and in seven others the scar was so thin that we were amazed they had not ruptured. Of these, two were of the low cervical variety.

Comments

1. Each case should be evaluated, and, even when there seems reasonable doubt, an x-ray will always guard against a possible abnormality.

2. The previous morbidity of patient, type of repair, or time interval seemed to have nothing to do with the type of scar.

3. In 41 repeat cesareans, where the operation was for disproportion, the succeeding babies weighed from 4 ounces to 2 pounds, 7 ounces more than the previous ones had. The heads had to be displaced out of the pelvis.

4. In 49 cases of repeat cesarean, the placenta was directly under the previous scar.

5. One patient went to full term with a tubal pregnancy and delivered a baby weighing 8½ lbs.

6. One patient developed an obstruction due to a loop of small intestine becoming attached to a bleeding point at the left cornu.

7. One psychosis patient ripped her wound open twelve hours after operation and pulled out her intestines yet recovered without incident.

8. One diabetic went into shock three times within the first forty-two hours and recovered without incident.

9. One patient, a primipara of 35 years, had a cerebral accident when in her second month. This is an extremely rare occurrence in pregnancy and particularly so with recovery of the patient. There was no apparent connection with the pregnancy as far as cause and effect were concerned. The condition was diagnosed as probable congenital aneurysm of the cerebral vessel. Cesarean was decided upon to avoid the strain of labor, with its attendant possibility of a second accident. The patient has made a sustained recovery but apparently is going to have some permanent paralysis of the left leg and left arm. The facial paralysis has almost disappeared.

In preparation of the patient, previous to the appearance of Demerol, we avoided the use of morphia altogether except where local anesthetic was to be used, because it seemed to affect the infant. At the present time, the patient is given 150 mg. Demerol and 1/150 grain hyosein, 30 minutes before operation, and we have thus far had no difficulty in resuscitation. There was not much in the way of anesthetic difficulty in the less common types. In one of the spinal anesthetic patients, the blood pressure dropped alarmingly for a short time. In one of the Pentothal, the patient stopped breathing on the table and the section was halted until respiration was again instituted. A curious thing happened in one of the Avertin patients. She was a good-sized patient and had a severe mitral lesion. She had been given 1/4 grain morphine before operation and 2/3 of the dose of Avertin per body weight. She did not become conscious until ninety-two hours after operation and seemed none the worse for the experience; indeed, the enforced rest had apparently aided the heart condition.

Morbidity.—Using the set rule of considering any patient morbid who had a temperature of 100.4° F. two days consecutively or more, the patients were divided as follows: 110 patients, or 21.5 per cent, were morbid at some time postoperatively. Twelve patients had temperatures up to 105.2° F.

These twelve had the following complications:

| | |
|-------------|------------------------|
| 1 Phlebitis | 6 Abscess in the wound |
| 1 Emboli | 4 Pyelitis |

Five of these patients had marked distention requiring stomach washing or the use of Wangenstein apparatus. In two patients the question of obstruction became a problem. After careful evaluation, 1 1/2 oz. of castor oil was introduced in the Wangenstein tube and the difficulty disappeared. With distention and vomiting, the decision requires attention to details and then courage. Since Demerol has been available, we use as much as 100 mg. every three hours for the first twenty-four hours after section and try to get patient on full diet by the third day. All patients are given peptorolysis of 5 per cent glucose until taking fluids freely by mouth and we feel that our patients are more comfortable now than previously by also omitting any postpartum pituitary extract with the exception of the initial dose.

Fetal Deaths.—

| | |
|---------------|---------------------|
| 5 Abnormality | 3 Melena neonatorum |
| 2 Prematurity | 2 Atelectasis |

Total of twelve in all . . . 2.4 per cent, 3 diagnosed before operation.

Maternal Deaths.—

1. Pneumonia. Entered hospital with lobar pneumonia of two days. This patient was a primipara, 19 years of age. She had a contracted pelvis, her membranes ruptured, and the medical consultant decided the operation would have to be risked -----1

2. Diabetic. Noncooperative. Had been in coma at sixth month and again late in seventh month -----1

3. Died of massive pulmonary embolism on the 2nd and 4th days, respectively. Both died within a few minutes after the sudden onset. Both these patients were primiparas of 22 and 27 years respectively. Both were in the eighth month and both had central placenta previa -----2

4. Peritonitis on the fifth day. In this patient, the referring doctor had reported no examination but rectal. On entrance, patient had ruptured membranes with about three-finger dilatation. At operation, the baby showed forceps marks, plainly indicating that an honest history had not been given -----1

THE OVARIAN HYPEREMIA REACTION: ITS USE IN QUALITATIVE AND QUANTITATIVE TESTS FOR URINARY CHORIONIC GONADOTROPIN

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AN ACCURATE method for testing for chorionic gonadotropin in the urine, using the ovarian hyperemia in the immature rat as the end point, was first reported by Reiprich¹ in 1933. Since that time, many other authors have reported a similar high degree of accuracy.²⁻⁸ Several workers have been unable to obtain a dependable accuracy with this method.^{9, 10}

The purpose of this report is to summarize our experience using this test. The method in use is modified in a few details from that employed in the laboratory of Dr. Emmanuel Klempner.¹¹ Also included are some results of a dilution procedure which permits use of the hyperemia effect as a means of estimating quantitatively gonadotropin excretion.

Methods

Qualitative Test.—Immature female white rats of the Wistar strain, weighing between 30 and 60 Gm., are used. The animals are kept at between 72 and 76° F. Two of these animals are injected subcutaneously each with 5 c.c. of concentrated morning urine, refrigerated until the moment of injection. The rats are killed with illuminating gas twenty-four hours after injection. This is not essential, but the carbon monoxide of the gas accentuates the hyperemia and makes the color reaction easier to evaluate. The ovaries, with a portion of the uterus and of their mesentery, are dissected free. Sufficient tissue must be left around the ovary to prevent drainage of the blood from the ovarian plexus, with subsequent blanching of the ovary. Excessive intraperitoneal bleeding should be avoided, since staining of the ovary with blood may be misleading. After gentle blotting of the ovary on moist gauze, the color is observed.

The amount of color of the ovary is the basis for the reading of the test. The color is best evaluated in daylight. The finding of one ovary of the two pairs which is bright red, i.e., as red as the kidney, is sufficient for a diagnosis of "positive." The presence of four pale white ovaries is interpreted as a "negative" test. When one or more of the ovaries is reddened to an extent more than will allow a diagnosis of "negative," but still is not as red as kidney, the test is reported as "equivocal."

In instances where a definite diagnosis cannot be made, for example, when the urine is toxic to both of the test animals, when one of the animals dies and the other animal is read as "negative" or "equivocal," or when the reading of the test is "equivocal," it has been found convenient and timesaving to request submission of another urine specimen for testing. Repetition with the same specimen usually gives a result similar to that obtained on the first test. Occasionally, detoxification of the urine with ether is necessary when another specimen cannot be obtained, but the detoxification is undependable and frequently is not effective. When a "negative" response is obtained in animals which appear moribund following injection of urine, the test is repeated. Toxicity is, in almost all cases, due to bacterial contamination of the urine.

10. Adhesions did not play a large role but the impression was that we were inclined to find more where there had been previous extraperitoneal sections.

Conclusions

Five hundred and ten cases of low classical cesarean section have been presented, an incidence of 2.3 per cent. A maternal death rate of 0.98 per cent and a fetal death rate of 2.4 per cent.

119 SOUTH HIGHLAND AVENUE

This author reports a very high incidence of false "positive" tests. Urinary gonadotropin of the nonpregnant individual causes a hyperemic effect reaching its greatest intensity in a few hours and tending to fade by 24 hours.¹² Chorionic gonadotropin causes an intense hyperemia at 24 hours which is certainly as intense and possibly more intense than that seen at two or six hours. The response caused by the injection of urine containing gonadotropin of the nonpregnant person has not, in our hands, been nearly as intense as that caused by the injection of urine containing chorionic gonadotropin. Therefore, we feel that the interval of twenty-four hours between injection and interpretation and the requirement of sufficient hyperemia to cause a color as red as the kidney for the test to be called "positive" eliminate many erroneous reports of "positive."

All the causes of the so-called "equivocal" reaction have not been discovered, but a few conclusions can probably be drawn. A considerably higher percentage of spontaneous abortions occurs in patients whose urine yields an "equivocal" result than occurs in the patients whose urines yield "positive" reactions. This increase in abortions—21 per cent following an "equivocal" reaction as contrasted with 8 per cent following a "positive" reaction—is probably significant, although it must be realized that absolute accuracy in follow-up records is not possible. It would seem possible that these patients are excreting a smaller amount of chorionic gonadotropin than is excreted by the patient with a normal pregnancy.

Several of the patients whose urines caused "equivocal" reactions and whose second urine specimen submitted a few days later caused a "negative" reaction may have been near the time of ovulation, since an apparently normal menstrual period occurred a little over two weeks after the date of submission of the first specimen.

The insensitive animal may also cause an "equivocal" reaction. Not infrequently one of the two rats has only a weak response, whereas the second animal of the pair has a strongly "positive" reaction. Our animals are kept between 72 and 76° F. at all times, since it has been found that increased temperature definitely decreases the responsiveness to gonadotropins. If the urine is toxic but not actually lethal to test animals, the sick animal does not have normal sensitivity to gonadotropins. If a "negative" response occurs in sick animals, the test is repeated.

Quantitative Test.—The excretion of gonadotropin throughout normal pregnancy has been determined by study of 14 patients. A rapid increase in daily excretion rate occurs during the first few weeks of pregnancy until a peak of about 12,000 or more rat hyperemia units per 24 hours is reached at about the 60th day. A fairly rapid decline then occurs until a relatively low rate of excretion at between 1000 and 4000 rat hyperemia units per 24 hours is reached at about the end of the first trimester. Excretion at this level is maintained throughout the last two trimesters of pregnancies. This is in agreement with the findings of Browne and Venning¹³ and Evans et al.¹⁴

In seven patients, the presence of a threatened abortion was suspected. Levels of gonadotropin excreted were 50 per cent to 75 per cent lower than are found in normal pregnancy of the same duration. As the abortion became inevitable, the rate of excretion rapidly declined. Death of all chorionic tissue was suspected when no gonadotropin was present in the urine. Abortion subsequently occurred in all seven patients. A lowered rate of excretion in patients with threatened abortion has been reported by other authors.^{11, 13} It is our belief that therapy is justified as long as the finding of chorionic gonadotropin in the urine indicates the presence of viable chorionic tissue. A falling level of excretion indicates the need for increasing the vigor of treatment. The absence of gonadotropin in the urine is an indication for stopping therapy. We are of

Quantitative Test.—Serial dilutions of a twenty-four-hour urine collection are given to pairs of rats. The reading of the test is carried out in the same manner as for the qualitative procedure. One "hyperemia unit" has been arbitrarily defined as the amount of material required to cause a definite "positive" response. This is equivalent to approximately three I.U. of chorionic gonadotropin.

Results

Qualitative Test.—The results of the first 703 tests, performed on specimens submitted by 595 patients, have been analyzed. For the total of 703 tests, 603 diagnoses were made. Three hundred and twenty-six tests (54 per cent) were reported as "positive"; 277 (46 per cent) tests were reported as "negative." There were 8 (1.3 per cent) erroneous diagnoses, of which 5 were falsely called "negative"; 3 were called "positive" when the specimens were submitted by patients who were not actually pregnant. The diagnosis was correct in 98.7 per cent of the tests. Of the total of 703 tests, 100 (14 per cent) tests did not provide a diagnosis. Fifty (7 per cent) were repeated because the urine specimen was toxic to the animals. Fifty (7 per cent) of the tests were reported as "equivocal." Repeated tests on the urines of the patients having "equivocal" tests resulted in a diagnosis of "positive" in 21 (42 per cent) and a diagnosis of "negative" in 20 (42 per cent). Seven (14 per cent) of the patients aborted before another specimen for testing could be obtained and 2 (4 per cent) had normal menstrual periods.

Of the eight erroneous results found in this analysis of 703 tests, five consisted of a reading of "negative" for the test on specimens submitted by patients who subsequently were found to have normal pregnancies, and three consisted of readings of "positive" for specimens from nonpregnant patients. Two of the erroneous "negative" tests may have resulted from the submission of specimens too early in pregnancy, since they were submitted at about the time of the first missed period. A third erroneous "negative" test was compared with the Friedman and the standard Aschheim-Zondek test, each of which was also read as "negative." It is felt that two of the erroneous "positive" tests may have been due to inexperience, since these errors occurred soon after this method of testing for chorionic gonadotropin was instituted in our laboratory. The record of each of these tests shows that the reaction was a "light red." In view of subsequent experience, reactions of this sort are now called "equivocal," and the test is repeated. In two tests performed after the statistics reported above were compiled, erroneous diagnoses of "positive" were made on urine specimens from patients found at operation to have corpus luteum cysts. Zondek, Sulman, and Black⁴ have also reported a false "positive" test in a patient with a corpus luteum cyst.

The accuracy of almost 99 per cent reported here is at variance with the accuracy reported by some other laboratories. There are three factors which may account in part for this discrepancy: (1) A greater volume of urine is used for injection than in other laboratories which have reported poor accuracy; (2) our animals are sacrificed twenty-four hours after injection, which tends to cause a more dependable ovarian reaction than the shorter tests⁷; (3) a definite diagnosis is not made in any case where a reaction greater than "negative" or less marked than a full "positive" is found. Since approximately 50 per cent of the patients having "equivocal" tests later develop "positive" tests, and 50 per cent develop "negative" tests, it is obvious that an arbitrary grouping of these "equivocal" tests into the "negative" group, such as was done by Bunde,¹⁰ introduces a considerable error.

The unpredictability of this method of testing for chorionic gonadotropin which was reported by Farris⁹ is overcome in part by the factors listed above.

2. Of the 100 tests for which no diagnosis was made, 50 were reported as "equivocal" and tested again later; 50 were repeated because the urine specimen was toxic to the animals.

3. Of the 50 tests reported as "equivocal," 28 (56 per cent) were submitted by patients who were later found to have been pregnant. Twenty-two (44 per cent) were from patients who were later found not to have been pregnant. The incidence of abortion was 21 per cent in the patients who submitted a specimen reported as "equivocal," whereas only 8 per cent of the patients having a test reported as "positive" subsequently aborted.

4. By a simple procedure involving serial dilutions, a roughly quantitative estimation of gonadotropin excretion can be made.

5. During normal pregnancy, a high peak of gonadotropin excretion is reached during the first trimester, with a decline of excretion to a relatively low level by the end of the third month. This low level is continued throughout the last months of pregnancy.

6. In threatened abortion, the excretion of gonadotropin is lower than for the normal patient at a comparable stage of pregnancy. A rapidly falling rate of excretion is an indication for more vigorous therapy. Death of chorionic tissue should be suspected in the absence of gonadotropin in the urine.

7. A high gonadotropin excretion late in pregnancy may be associated with toxemia.

8. A patient suffering from a chorionepithelioma with metastasis had a very high excretion of gonadotropin before death.

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the opinion that following patients in this manner eliminates much useless therapy.

Two of the patients whose gonadotropin excretion was studied throughout pregnancy developed definite, though not severe, symptoms and signs of pre-eclampsia. In both of these patients, a definite increase in gonadotropin excretion occurred several weeks before any other objective signs developed. In one of these patients, a diabetic, the level of excretion was as high as 15,000 rat hyperemia units per 24 hours during the eighth month when the normal excretion is not over 4,000 units. In the other patient, an excretion of 6,000 units per 24 hours was maintained for several weeks before the onset of symptoms of toxemia. A patient with severe toxemia, whose condition necessitated interruption of pregnancy, excreted over 12,000 rat hyperemia units per 24 hours. Two other patients with severe pre-eclampsia also had high titers averaging 12,000 units per day. Gonadotropin excretion was normal in another patient who developed edema and was suspected of having pre-eclamptic toxemia. The edema cleared completely without development of any other signs of toxemia following a few days of bed rest, fluid restriction, and low-salt diet. A patient with chronic nephritis and hypertension had a normal rate of excretion.

The elevation in gonadotropin levels in patients with pre-eclampsia or eclampsia, as reported by Smith and Smith^{15, 16, 17} can be easily recognized. We have, as yet, no explanation for our finding of an increased excretion in the urine before the appearance of signs of toxemia when these authors could detect this rise only in the serum and not in the urine until the toxemia became evident.

Excretion of gonadotropin by a patient with a chorionepithelioma with metastasis, the diagnosis of which was confirmed by the finding of chorionic gonadotropin in fairly large amounts a month after delivery, reached levels of over 16,000 rat hyperemia units before death. Tumor tissue removed at autopsy contained a high concentration of gonadotropin. The high level of gonadotropin excreted by this patient is in complete agreement with many previous reports in the literature.⁴

In three brief case reports—two of patients with hydatidiform moles and one of a patient with a chorionepithelioma—Zondek et al.⁴ mention the estimation of the amount of the ovarian hyperemia-producing factor in the urine. No details of procedure are included. The values reported by these authors are much higher than the values found in any of our studies. It is possible that this difference may be due, in part, to a difference in animal sensitivity, but it is most probable that a difference in end point is the most important factor. For the sake of uniformity, we have set up our end points as a definite bright red. Many times, a less intense reddening of the ovary occurs in animals which have received higher dilutions, indicating that some gonadotrophic effect undoubtedly has occurred. It has been our impression that this slight reddening is too indefinite and unpredictable to be a useful end point.

The value of this method of quantitatively estimating chorionic gonadotropin is its simplicity, and we feel that it has sufficient accuracy to have clinical usefulness. Expense to the patient is low enough so that consecutive determinations can be frequently performed. Although absolute values are not comparable, the patterns of excretion are similar to those obtained with other methods.

Summary

1. In 703 qualitative tests performed on urine for the presence of chorionic gonadotropin, a definite diagnosis was made in 603 instances. Of the 603 diagnoses made, 595 (98.7 per cent) were correct.

crystals further as an easy conservative surgical procedure in pelvic inflammatory disease and for asymptomatic tubal block in sterility cases.

Application

The procedure is employed in two types of cases. First, those who have had complete infertility studies and in whom tubal occlusion was the most important factor. Roentgen evidence is often sought to demonstrate the point of occlusion although we do not make a routine practice of this procedure. (Fig. 1.) None of our cases have revealed an occlusion at the isthmus nor have we encountered in this small series salpingitis isthmica nodosa. From our observation it would seem that the vast majority of old salpingitis cases are blocked at the fimbria.



Fig. 1.—Typical view of tubal occlusion at the fimbria.

The second group of cases where the operation was employed was in chronic or recurrent gonorrhea. The chief complaint in these individuals was chronic pain and/or menometrorrhagia. The adnexa were fixed by adhesions, thickened, fimbria occluded, and often the uterus fixed in retroversion. We were operating here for relief of symptoms and not to cure infertility.

Technique

This procedure has not been materially altered since the original case. It is often necessary to do a lysis of adhesions to uncover the pelvic viscera. The uterus and adnexa are freed from the adhesive bed again by sharp dissection. The tubes are next freed from all but their natural attachments. The closed fimbria are grasped with Babcock visceral clamps and held by slight tension while a careful stab incision is made in what appears to be the ostium. This opening is gently enlarged with a long Kelly hemostat acting as a dilator, if the tube is not already dilated. A blunt probe is passed down to the isthmus and this is almost always possible if a proper salpingolysis has been done. Holding the tubal lumen open with a long tissue forceps, sulfanilamide crystals are poured into the tube and the excess up to 5 Gm. allowed to fall into the pelvic cavity. (Fig. 2.) A suspension is done if the uterus is retroverted. The abdomen is closed without drainage and a Rubin test is done two weeks following operation.

A TECHNIQUE FOR RE-ESTABLISHING TUBAL PATENCY*

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IT WOULD be a tremendous task, indeed, to describe all the operations that have been devised for the correction of tubal occlusion. Many operations for this cause of infertility have been forgotten. There are several worth-while operative procedures, however, that have been fruitful and should not be abandoned. The technique to be described involves old surgical principles with the addition of one adjunct, i. e., sulfanilamide.

In 1942 Beecham and Friday,¹ in a report on the local tissue reaction to sulfanilamide established that: First, the only harmful effect from sulfanilamide application locally in the abdominal wall, pelvic, or abdominal cavity occurred where the crystals are used in fatty tissue. When sulfanilamide crystals came in contact with fatty tissue that had been disturbed there was a resulting necrosis and a typical foreign-body response. Second, locally, sulfanilamide had a distinct styptic action. Third, experimentally, local sulfanilamide implantation caused a reduction of postoperative adhesions. With these results in mind, one of us (C. T. B.) has used sulfanilamide crystals in the pelvis almost routinely since 1941. The aforementioned conclusion from experimental work in animals have been borne out in everyday operative work. Falk and Bliniek² speak of using sulfanilamide crystals to "minimize the possibilities of postoperative intestinal adhesions." As far as we know, this is the only outside confirmation of the observation on a lowered incidence of adhesions following sulfanilamide over the peritoneal operative site.

The applicability of local sulfanilamide in the treatment of tubal occlusion was revealed to us in the following manner:

Miss B. B., aged 19 years, was operated upon by C. T. B. at Temple University Hospital Dec. 4, 1942. At that time, a tubovarian abscess about 9 cm. in diameter was removed on the right side. The left tube and ovary were bound down in the cul-de-sac. The tube was three times its normal diameter, being moderately thickened. The fimbria were closed and the entire structure closely adherent to the ovary. The picture was one of chronic or recurrent gonorrhea. A salpingolysis was done. The fimbriated end of the remaining tube was cut open preserving the fimbria and a probe passed to the uterine cornu. Sulfanilamide crystals were then poured into the tubal lumen. Five Gm. of crystals were used in and around the tube.

The patient married shortly thereafter, conceived, and was delivered, twenty-one months after the operation, of a full-term, normal fetus.

The reason we had tried the above technique in the operating room was simply to attempt some rational conservative procedure in a young girl. We had hoped only to salvage the adnexa, not thinking that the patient could ever conceive. The surprising result led us to employ the intratubal sulfanilamide

*Presented at a meeting of the Philadelphia Obstetrical Society, Dec. 4, 1947.

often condemned today. In general, one may gather from the works of Solomons,³ Greenhill,⁴ Lovset,⁵ Lastra and Jakob,⁶ and Siegler⁷ that the average success is approximately 10 per cent. Salpingolysis has been successful in approximately 10 per cent of cases when employed although Siegler reports a 17 per cent success. Tubal patency following this operation of salpingolysis and sulfanilamide application is comparable to the figure found in a series by Sovak,⁸ where conception results were not given.

It would seem from this series that salpingolysis is the operation of choice, with the added step of sulfanilamide crystal implantation. The salvage rate is higher than in other series of comparable operations.

In addition, this technique seems applicable to the old chronic pelvic inflammatory lesion where we have long-standing pathology in young women and we have no desire to sacrifice the adnexa.

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Discussion

DR. NEWLIN PAXSON.—This interesting paper presents a new idea based on sulfanilamide application, which may be useful in destroying adhesions within the abdomen. It is based on their original work published in 1942. The high incidence of pregnancy that one would not normally expect following surgical procedures, and the second inference, that of absence of ectopic pregnancy, would suggest the restoration of tubal patency. Although the group is too small to draw final conclusions the results are interesting. It would be well for all of us who do plastic operations on tubes to use sulfanilamide and send our results to Dr. Beecham so that he could collect a large enough series to assemble statistics. As soon as a study of this type is reported, it would be well to have hysterosalpingography before and after operation because its success could be proved in that way.

DR. SIGMAN (Closing).—Our method has been a conservative approach to this subject and that, of course, is what we always want in pelvic surgery. The operations and surgical approaches to tubal blockage and infertility as a whole have been very discouraging. Most recent reports that I could discover in the literature have ended up with a very discouraging report that the surgical approach is unsatisfactory. Yet I think all of us must consider one fact, and that is that there are a certain group of patients who will continue to come in search of alleviation of sterility.

There was only one other interesting piece of work in re-establishing tubal patency by pharmacosurgical methods being done by a group in Stockholm. Penicillin was inserted in the tube and followed later by injecting penicillin retrograde into the tubes every 12 hours. They have reported an occasional successful case; they do not yet have a series of cases. The second method by the same group is, at laparotomy after tubal patency is secured, to place cholesterol wax in the tube and close the abdomen. After operation, a vaccine is given to raise the body temperature to 104° F., melting the wax, which absorbs, and leaves the tubes patent. This too is still in the experimental stage. I feel that our method, inserting sulfanilamide powder into the tubal lumen, is a conservative approach and offers good results.

Results

Eight patients have been subjected to operation for infertility due to tubal block. Of these eight, two have conceived and delivered at term for a 25 per cent successful result. Seven of the eight have consistently demonstrated patent tubes at a normal pressure. In one of the eight, the tubes have remained closed. Only one complication was noted in this group of eight patients and that was a flare-up of an old gonorrheal inflammatory disease. This patient needed a colpotomy three weeks after operation but since then has demonstrated tubal patency at 60 mm. of mercury.

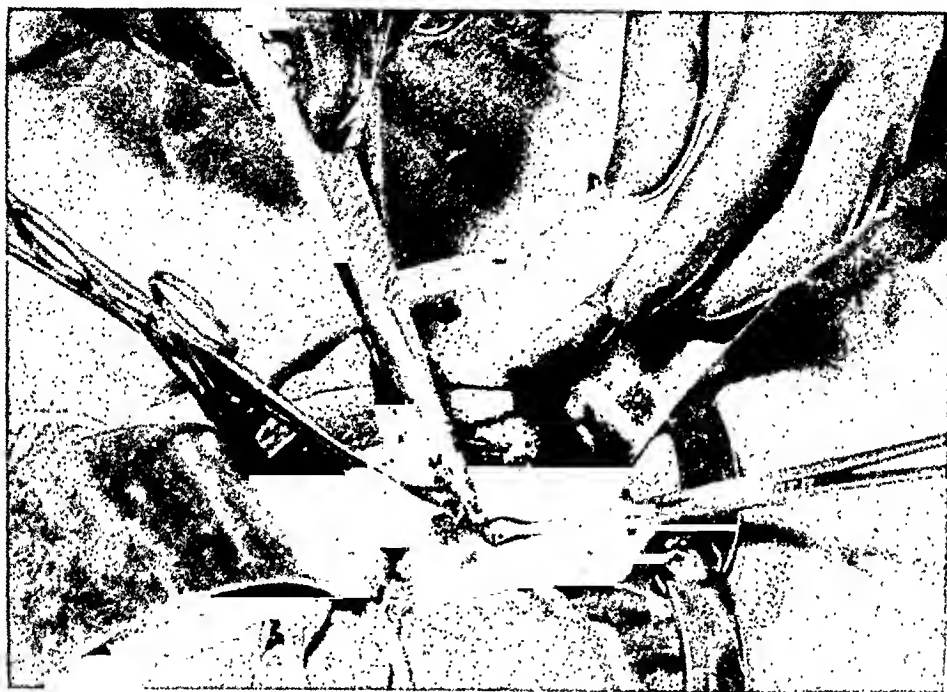


Fig. 2.—Fimbria held with visceral forceps, long tissue forceps in the tubal lumen, and sulfanilamide crystals being introduced.

A second group subjected to this operation consisted of ten patients with adnexal pathology, for the most part gonorrheal in nature. These patients all had pelvic pain that was incapacitating enough to warrant surgery. Three of the ten had tubovarian endometriosis with tubal block. Of these ten operated upon, two have conceived, one delivered at term, and one aborted. Three of the ten patients have closed tubes in spite of being asymptomatic, while one has been lost sight of and we have no follow-up. One of the ten had a mild flare-up of the pelvic inflammatory disease. She is symptom free now and her tubes are open.

In those operated upon primarily for infertility we have had a 25 per cent success. In those operated upon for pelvic symptoms and not to relieve infertility, we have obtained a 20 per cent success as far as conception goes, although one of these cases aborted spontaneously at two months. There were no ectopic pregnancies encountered in the group.

Discussion

From a review of the literature, it is quite evident that tubal occlusion at the fimbriated end offers the greatest chance of success in plastic surgery. Results in the past have not been good and consequently the operation is all too

performed interposition operation. It helps ensure the permanence of the correction of the prolapse and almost eliminates the possibility of the development of cervical carcinoma in the future.

A few gynecologists claim that interposition of the uterus under the bladder increases the likelihood of urinary complications. While some patients do have difficulty in voiding spontaneously and may need repeated catheterizations, this is equally true of women on whom a vaginal hysterectomy or the composite operation has been carried out. An occasional case of postoperative cystitis develops, but, if recognized promptly and treated with chemotherapy, the infection almost invariably clears up in a few days. There is no record in our series of a permanent bladder disorder being caused by an interposition.

Some members of the staff place indwelling catheters in the bladder for from a few days to over a week. Others prefer repeated catheterizations until the bladder regains its tone. All agree that it is most important to avoid overdistention of the bladder. In recent years, the writer has gotten all of his patients in satisfactory condition out of bed on the second postoperative day, and even on the day of operation, if the patient is unable to void lying down. He has a firm conviction that, by doing so, the need for repeated catheterizations has been reduced.

Before presenting the results of this study of 145 women operated on since 1931, the previous reports on the interposition operation by the gynecologic staff of the Johns Hopkins Hospital will be briefly reviewed. The first of these was by H. N. Shaw, and was based on 118 operations performed between 1900 and 1921. However, only 58 of these patients were traced. This is understandable, as many of the women in the series were of the dispensary class, who frequently changed their residences. Also our social service follow-up was then in its infancy.

During the first two decades of this century, the contraindications to the interposition operation were not appreciated by all operators. For instance, in Shaw's series, 34 women were under forty years of age when operated upon. Moreover, the operation was performed on two women in whom future pregnancy was possible and, incredible as it may seem, one of them did later deliver a ten-pound baby. From about 1915 on, all gynecologists began to realize that the use of the operation should be restricted almost entirely to the treatment of patients near or subsequent to the menopause.

Because of the early lack of awareness of the limitations of the interposition operation, it seems fair, in an attempt to evaluate this surgical procedure, to eliminate from Shaw's series all those patients operated upon prior to 1914. If this is done, we find that Shaw was able to trace 21 of the women operated upon in the Johns Hopkins Hospital between 1915 and 1921. There was only one failure in this group.

The second study was made by the present writer and reported in 1926. It dealt with the results obtained by Dr. T. S. Cullen at the Johns Hopkins Hospital and Church Home Infirmary and with those obtained by the author himself. In all, 56 patients were studied. No patients in this series became pregnant later. There were no postoperative deaths. Two patients had postoperative bleeding from the perineum. This was easily controlled. One developed a chronic cystitis which worried her for several months. Today, chemotherapy would doubtless give prompt relief in a similar case.

IN DEFENSE OF THE UTERINE INTERPOSITION OPERATION

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THREE previous reports from the gynecologic department of the Johns Hopkins Hospital, published in 1922, 1926, and 1935, have dealt with the results obtained by the staff with the Watkins' interposition operation in the treatment of uterine prolapse. This fourth report is a further study and critical evaluation of the results of this operation since 1930 and is prompted by the author's conviction that the operation has an important place among gynecologic procedures. It is not to be inferred that it should always be carried out in the surgical correction of uterine prolapse. There are more vaginal hysterectomies, Manchester, Spaulding-Richardson composite operations than interposition operations performed in the Johns Hopkins Hospital at the present time. Indeed, the name of one member of the staff, Edward H. Richardson, is associated with the development of the composite operation. His reports and those of Telinde have emphasized the good results obtainable with this procedure.

Our experience with the interposition operation during the past seventeen years suggests that its recent marked loss in popularity is unwarranted and that many criticisms of it are unjust. For example, when one reads of a pregnant woman whose uterus has been interposed under the bladder, having difficulty with delivery, it is not the operation, but the operator who should receive the criticism. There is never any excuse for performing an interposition on a woman in the child-bearing age and leaving her with the possibility of becoming pregnant.

Some of the critics of the operation point out that uterine cancer may still develop postoperatively at any time. This is true, but as there is no record of its occurring in a single case operated on at the Johns Hopkins Hospital, its incidence must be low. One must remember that a malignancy reported developing as early as twelve or even eighteen months after an interposition operation may have been present and overlooked at the time of the operation. The operation should not be performed on a woman with metrorrhagia unless some benign explanation for the bleeding, such as a cervical polyp, is found and the possibility of malignancy ruled out; nor should the operation be selected for women with excessive menstrual bleeding.

A dilatation of the cervix and curettement of the endometrium should always be the first steps in performing an interposition operation. Whenever an excessive amount of material is obtained or the consistency of the curettings suggests malignancy, the correction of the prolapse should be delayed until a microscopic report is obtained. Although there are in our series a few cases in which the cervix was not amputated and the prolapse still was corrected, the majority of the staff feels that an amputation is an integral part of a properly

second, a 67-year-old woman, but she was carefully studied by the medical department postoperatively, and a diagnosis of coronary thrombosis was made. This second fatality might have occurred even if there had been no operation.

The nonfatal postoperative complications consisted of 13 infections of the bladder, all of which cleared up under chemotherapy, and of two instances of thrombophlebitis. Fortunately, the two latter were mild in character and were giving the patients very little discomfort when they were discharged from the hospital. In only one patient did any postoperative bleeding occur, and this was not profuse. It came from the anterior vaginal wall and was easily controlled.

Of the 143 women who survived the operation, 115 (80 per cent) were heard from between October 1, 1947 and January 1, 1948. Eighty-four have been examined. The operation completely relieved the symptoms of prolapse, cystocele, or rectocele in 110 of the 115 cases followed (95.6 per cent).

A review of the small percentage of the cases in which there was a partial or complete failure is of importance from the standpoint of bettering future results. One woman, 11 years postoperatively, had a return of the rectocele without any uterine prolapse or cystocele. This was corrected surgically. Another woman, after two years, noticed that she could feel her cervix at the vaginal orifice; but this gave her no discomfort and no further treatment was carried out. The two above-mentioned cases might be classified as partial failures. One patient had a return of the prolapse within a year, and a Le Fort operation was then done. A second woman, 70 years of age when operated upon, replied to a questionnaire sent her four years after she had left the hospital that she was in perfect health, but then wrote again a few months later stating that she had had a severe fall following which the prolapse returned. In a third patient, the interposition operation held for 11 years, but then there was, rather suddenly, a marked return of the prolapse. These three cases are considered complete failures even though in one, relief was obtained for four years, and in another, for eleven years.

Only four of the 113 patients were under forty years of age when operated upon. These figures are a marked contrast to Shaw's report dealing with the patients operated upon during the first part of the century. The four patients in this present series were between 30 and 35 years of age. They have been checked in the past few months and, in all, the uterus is in excellent position. Nevertheless, the author feels that an interposition should not be performed in a woman under forty. All the young women in our present series were operated on over twelve years ago. Today, some other operation for the prolapse would be performed.

A direct question about dyspareunia was asked nearly all the women who were examined. Only two complained of it and in them it was due to a too snug perineorrhaphy. Many of the women we have examined in the past few months are now well advanced in age, so the information obtained about dyspareunia is not entirely reliable.

The average number of years since the interposition operations were performed in the patients whom we have traced is between seven and eight. More than ten years have elapsed since 33 of the women were operated on and more than five years since 88 had the interposition. These figures are strong evidence of the permanency of the correction of uterine prolapse by the operation.

Of the 110 patients on whom the operation was a complete success, four have now died of medical conditions in no way associated with the operation. One died at 76, six years after the interposition. A second died at 70, five years after the surgery; a third died at 69, four years postoperatively, and a fourth at 71, after enjoying 12 years of good health following the operation.

One hundred and eight women are known to be living and well at the present time. Four of these are over eighty years of age, thirteen between 75

Forty-eight of the 56 patients, or 85 per cent, were traced. Forty-five women reported that they were relieved of all their symptoms and a large percentage of these were examined and found to have no evidence of prolapse. Three of the forty-eight felt that the results were not entirely successful, but only one had to have a second operation. She developed a cystocele eleven years after the first operation. In brief, 45 out of the 48 women traced, or 93 per cent, made a complete recovery and were relieved of all their symptoms.

The third report, by Everett, was based on a study of 68 patients. One died of pulmonary embolism. Sixty-seven were discharged as well. Everett was able to get data on the ultimate outcome of 48 of the 67 patients. Forty-six, or 95 per cent, showed excellent anatomic results. In two cases, after five years of complete relief, there was a recurrence of moderate prolapse. Three complained of dyspareunia, but this was due not to the interposition, but to a too snug perineorrhaphy.

This, the fourth report of our results with the interposition operation, is a study of 145 patients operated upon in the past seventeen years. This number includes all patients on whom this operation was performed in the Johns Hopkins Hospital by the gynecologic staff and also some additional private patients operated on by the writer at other Baltimore hospitals.

In 141, the operation was performed for uterine prolapse. The degree of descensus was moderate in 34, marked in 50. There was a complete, or what is sometimes called a third-degree, descensus in 57. In two, there were large cystoceles without any procidentia. In two, the body of the uterus had been previously removed by a supravaginal hysterectomy, and in later years the cervical stump had prolapsed. In these two, the interposition principle was followed, but instead of the uterine body, the cervical stump was interposed under the bladder.

As the great majority of women in this study were beyond the menopause, we find records of only six sterilizations. No patients later became pregnant. Thirty-five women were over 60 years of age. Twenty were over 65, and four over 70, which indicates that age itself was seldom considered a contraindication to this operation. On general physical examination, a systolic blood pressure of over 180 was found in six women. This series also included two diabetics with cases of moderate severity, both of whom had uncomplicated convalescences.

Six patients had enteroceles in addition to the uterine prolapse. Small myomas were present in thirteen uteri. At operation, the myomas were removed at the same time as the interposition operation was carried out. Only when the patient is at or beyond the menopause and the tumors small is this recommended. Under other conditions a vaginal hysterectomy is advisable.

The only serious operative accident was the perforation of the bladder in one case. The opening was immediately closed, and the patient had no post-operative difficulty, not even developing a cystitis. In one case, the body of the uterus was traumatized to such extent in being delivered, that a partial fundectomy was added to the interposition operation.

A cervical amputation was carried out in 132 cases. Microscopic study of the removed cervixes showed hyperkeratosis in 18 and squamous metaplasia in 12. Almost all showed infection, the pathologic report varying from slight to marked endocervicitis. In one patient operated upon in 1934, the cervix showed a very early squamous-cell carcinoma. As the patient was 61 and it was felt that the amputation had been sufficiently high to give considerable margin above the malignancy, no further treatment was advised. It has now been 13 years since the operation, and the patient is still enjoying good health at the age of 74.

There were two operative deaths. One woman died on the fourteenth post-operative day and the other on the thirteenth. An autopsy of the first case showed an extensive pulmonary embolus. No autopsy was obtained on the

THE LEFORT COLPOCLEISIS: AN ANALYSIS OF 43 OPERATIONS*

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PROLAPSE of the uterus and the associated descent of the vagina, being the consequences of developmental defects and childbearing trauma, have always engaged attention. Recently it has been emphasized that procidentia may not only give rise to ureteral kinking and secondary hydronephrosis,¹ but may also be the cause of hypertension.²

Extensive operations for the correction of uterovaginal prolapse in women who are still in the childbearing age should obviously be avoided. Fortunately, most instances of annoying first- and second-degree prolapse occur after the childbearing age, during the premenopausal, fifth decade of the woman's life. Complete prolapse is most common after 60 years, when postmenopausal genital atrophy has already occurred. Following the accepted trend in gynecology, we avoid abdominal operations and attempt to treat all patients with uterovaginal prolapse by the vaginal route. In the postmenopausal patient, whose state of health demands as little surgical procedure as possible and in whom the coital function is not essential, an almost complete vaginal closure, the so-called Lefort colpocleisis is our operation of choice.

The advantages of the Lefort operation include the rapidity and ease of its performance, even under local anesthesia, factors of inestimable value in avoiding undesirable shock and trauma in elderly women who are unfit for more extensive operations. The principal disadvantage is that in the event of vaginal bleeding there are no means whereby one may determine the cause of the bleeding without abdominal hysterectomy. Lefort's first operation was performed in two stages, the resulting inverted U-shaped channel was sufficient to permit sexual intercourse. Indeed, his first patient was later delivered of a living, almost full-term child, after incision of the previously contrived septum.³ The first colpocleisis in the United States was performed in 1880 in Boston by Dr. Fanny Berlin.⁴ Since then, the operation has been variously modified, especially in regard to the type of lateral channel and the repair of the pelvic floor, and has been evaluated by several gynecologic clinics.⁵ It is a relatively simply surgical procedure, one admirably suited to elderly women in whom more extensive operations are contraindicated. It deserves a limited application in the treatment of prolapse.

An Analysis of 43 Lefort Operations

The present report comprises a critical analysis of 43 instances of genital prolapse treated by means of almost complete colpocleisis at the Mount Sinai Hospital during the thirteen-year period, 1934 to 1946, inclusive. The indication for the operation in each patient was the presence of complete genital prolapse. Of the 43 patients, 36 (83.7 per cent) had had procidentia for from six months to thirty years; the remaining 7 (16.3 per cent) had suffered from vaginal prolapse for from four to twenty-five years following hysterectomy.

*Presented at a regular meeting of the Philadelphia Obstetrical Society, Nov. 6, 1947.

and 80, and thirty-four, 70 or over. Many elderly women who have interposition operations live on afterward for many years. It is important to emphasize this. Not infrequently the families of elderly women advise against surgery because, as they say, "Grandmother is not going to live many years anyhow, and so why worry her?" The author has no more grateful patients than these elderly women who have had their uterine prolapse corrected surgically. They seem to take a new lease on life.

Having now presented the results of the interposition operations since 1930, the author believes it would be of interest to add to the figures just given those in the three previous reports from the gynecologic staff, omitting the cases in Shaw's series operated on prior to 1915. Two hundred and ninety operations were performed with three operative deaths. However, one fatality was due to coronary disease, and might have occurred even if the patient had not been operated on. The other two were the result of pulmonary emboli. There is the possibility that by getting patients out of bed on the day of operation or at least on the second postoperative day, the danger of embolus is much decreased. In the past five years, the majority of my gynecologic patients have been out of bed early and, during that time, only one small embolus was observed from which the patient quickly recovered.

Out of the 287 women surviving operation, 232 were traced (80 per cent). Of these, 221 were completely relieved of all their symptoms. This gives a percentage of 95 per cent of complete success with the interposition operation on those patients followed.

The operations on eleven women are classified as failures and make up the 5 per cent of unsuccessful operations. However, one woman has no symptoms and merely has noticed that when she stands she can feel the cervix at the vaginal orifice. Three other women were well for ten years and then had to have a second operation; one for prolapse of the uterus, a second for a cystocele, and a third for a rectocele. Possibly some of these ten cases should not be considered as complete failures. This study indicates the necessity of a long term follow-up of patients operated on for uterine prolapse, since some of the recurrences in the series occurred after as long as ten years.

Summary

1. Since 1931, uterine interposition operations have been performed on 145 patients at the Johns Hopkins Hospital. The results obtained have been presented.

2. These figures have been combined with the figures cited in three previous reports by the gynecologic staff of the Johns Hopkins Hospital.

3. The results obtained show that the uterine interposition operation is satisfactory for uterine prolapse in women at or beyond the menopause.

4. The author does not claim that the interposition operation is the procedure of choice in all cases of uterine procidentia, but points out that in his hands and in those of the other members of the Johns Hopkins gynecologic staff, it has yielded a high percentage of successes.

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Operative Technique

The 43 LeFort operations herein analyzed were performed by the authors with little variation in the technique. The anesthesia employed was selected according to the individual needs and included spinal, caudal, ether inhalation, intravenous pentothal, and local infiltration with 1 per cent solution of novocaine. A perineorrhaphy was included in each operation, and, in twelve instances, as noted previously, amputation of the cervix was also done. The cervical amputations were of the circular type and constituted the initial phase of the operation.

TABLE I. INCIDENCE OF COMPLICATING CONDITIONS IN 43 PATIENTS SUBJECTED TO THE LEFORT OPERATION

| ASSOCIATED CONDITION | NO. OF PATIENTS | PERCENTAGE |
|-------------------------------------|-----------------|------------|
| I. Medical: | | |
| Hypertensive cardiovascular disease | 17 | 39.5 |
| Diabetes mellitus | 5 | 11.6 |
| II. Surgical:* | | |
| Chronic cervicitis | 12 | 27.9 |
| Hemorrhoids | 2 | 4.6 |
| Fibroadenoma of breast | 1 | 2.3 |
| Varicose veins | 1 | 2.3 |

*Each was surgically corrected at the time of LeFort operation.

The LeFort operation begins with the denudation of the anterior vaginal wall, the cervix being drawn downward by means of traction sutures. A rectangular, snowshoe-shaped area of vaginal mucosa is excised, extending from 2 cm. above the external os to within 1 cm. of the external urethral meatus. The posterior vaginal wall is denuded in a similar manner with the important exception that the lowermost portion of the rectangle joins the butterfly-wing type of denudation required for the perineorrhaphy. Thus, a strip of vaginal mucosa, approximately 2 cm. in width, remains across the portio and continues laterally, widening as it nears the introitus on each side.

Beginning with the transverse strip of mucosa of the portio and following with the lateral strips, the anterior and posterior margins of the vaginal mucosa are sutured to each other with interrupted catgut sutures (No. 1 chromic). The latter are so placed that they both enter and emerge on the mucosal surface, permitting the knots to lie within the new vaginal channel. As the edges of the portio are sewn together, the cervix disappears from view and the uterus recedes upward. During the operation, the relaxed posterior vaginal wall is repaired in the usual manner. The mucosa-lined, inverted, U-shaped channel finally extends upward from one side of the introitus to the opposite side. The transverse bar of the inverted U-shaped channel is below the cervix.

In the twelve patients in whom the cervix had been amputated and reconstructed as the first step in the operation, drainage was established by several strands of silk-worm gut extending the entire length of the inverted U-shaped channel. These were withdrawn at the end of the first postoperative week.

The care of the patients postoperatively is not exacting. The only special measure is the daily instillation of one-half ounce of a 2 per cent aqueous solution of mercurochrome into the channel by means of a small catheter and syringe. The patients are encouraged to be active and are permitted to be out of bed on the third postoperative day. A full diet is allowed as soon as the patient desires. Bowel function is encouraged with mineral oil. An enema is given on the second postoperative day. Hospitalization is generally less than two weeks.

Marital Status and Age of the Patients

The importance of carefully explaining the antieoital nature of the operation to the patient cannot be overestimated. It should be painstakingly elucidated preoperatively, irrespective of the patient's age and marital status. One of our patients, a 58-year-old divorcee at the time of the LeFort operation, returned four years later as a newlywed and reasonably requested that the vagina be reconstructed for coital function. The primary prerequisite for the LeFort operation is that the sexual life of the patient must be completely and irrevocably renounced. If the patient is still married, it is imperative that the consent of the husband be obtained, irrespective of his age. In this series of 43 patients, 20 (46.5 per cent) were married, 20 (46.5 per cent) were widowed, and 3 (7.0 per cent) were divorced. Only one patient of the 43 was under 50 years of age; the majority were well over sixty (Fig. 1).

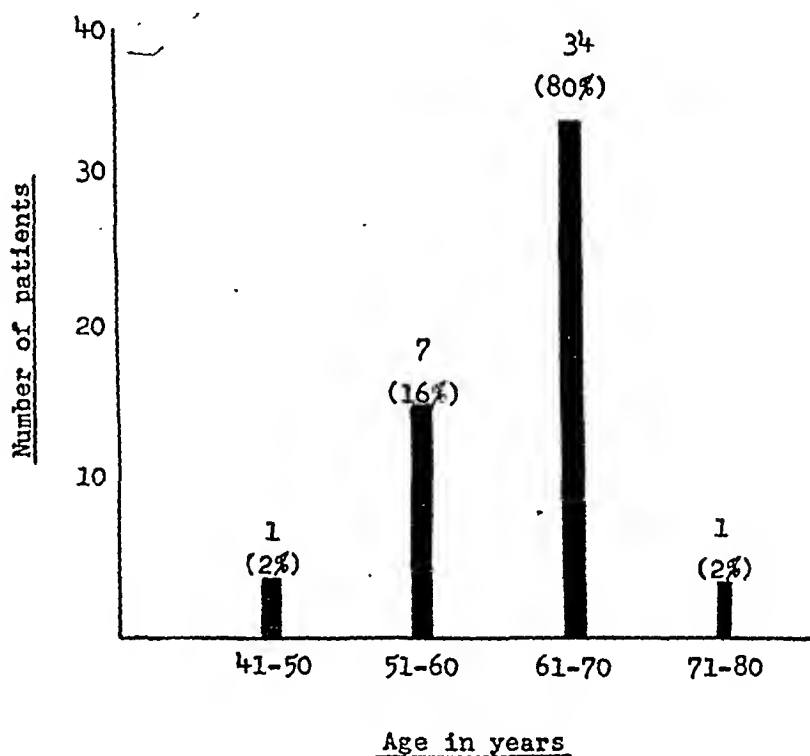


Fig. 1.—Age incidence of 43 patients subjected to the LeFort operation.

Associated Conditions

The complicating conditions customarily found in elderly women were encountered in one-half of the group (Table I). Seventeen of the 43 patients (39.5 per cent) had hypertensive cardiovascular disease of varying degrees. Six of these 17 were definitely poor surgical risks. Five of the series (11.6 per cent) had diabetes mellitus, requiring special pre- and postoperative care.

Conditions requiring additional surgical procedures at the time of the LeFort operation were present in 16 of the 43 patients. The most frequent of these was chronic cervicitis which required amputation of the cervix in 12 of the 36 patients in whom the uterus was present. Hemorrhoidectomy was indicated on two occasions; excision of a mammary fibroadenoma was performed once; and bilateral ligation of the saphenous vein was necessary in one patient.

the incidence of carcinoma of the uterine fundus is not so high, especially in women beyond the age of 65 years, to be a deterrent to the use of the LeFort operation when definitely indicated.

Summary

1. The principles underlying the surgical treatment of uterovaginal prolapse are briefly enumerated.
2. The indications for the LeFort colpocleisis, as one of the forms of surgical treatment, are stated, and the history of the operation reviewed.
3. The results attained in 43 patients subjected to the LeFort operation are analyzed, noting an anatomic failure in one patient and a functional failure in another.
4. The authors' technique of colpocleisis, including a circular amputation of the cervix as part of the operation when indicated, is described.
5. A singular disadvantage of the operation is the later inaccessibility of the uterus in the event of subsequent metrorrhagia, as evidenced by the histories of three patients in the group of 43 reported. The importance of avoiding estrogen administration for fear of inducing diagnostically disturbing, uterine bleeding in women who have had a LeFort operation is emphasized.

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Discussion

DR. BENJAMIN LEFF.—The advantages of partial colpocleisis are that the operation is not time consuming and may, if necessary, be done under local anesthesia. Since many of these patients are old and poor surgical risks, these are items of no little importance. In contrast to the advantages, its disadvantages are, first and foremost, that the uterus is encased back of a closed vaginal vault with only a narrow, and at best, inadequate channel for drainage. Subsequent pathology developed in the uterus is not likely to be discovered early, and is difficult to treat. The operation is palliative and does not in any way correct the distorted anatomy causing the condition. The uterus is given a shelf on which to rest within the vaginal tube. The attenuated ligaments and the retrodisplacement of the uterus, which exist in most of these cases, remain the same. It is noteworthy that of the 38 cases followed up, three developed metrorrhagia, an incidence of 8 per cent.

Because of the disadvantages stated, we have not favored this operation. On several occasions, when the patient's physical condition warranted, we have done total colpocleisis following vaginal total hysterectomy. When the patient's condition does not warrant subjecting her to the hazards of anesthesia, we are in accord with Emil Novak, who states, "I feel that when the condition of the heart, lungs, or kidney is sufficiently grave to contraindicate general anesthesia, the operation is rarely justified, and it is better to treat the patient palliatively with a pessary."

Results

No mortality occurred in this series of 43 patients. Ten of the group (23.2 per cent) presented postoperative complications as follows: urinary tract infection in five, fever of undetermined origin in two, infected perineorraphy wound in one, pneumonia in one, and coronary occlusion in one. Excepting the prolonged stay of these ten patients, the average number of hospital days for each patient was thirteen. At the time of discharge from the hospital, the functional and anatomic results were excellent in all patients.

Thirty-eight of the 43 patients were followed up satisfactorily for from two to eleven years. There was only a single failure—recurrence of the prolapse during the first postoperative year in a 68-year-old woman who had had a vaginal hysterectomy four years prior to the LeFort operation. She was subsequently cured by means of *total* vaginal closure. One patient, though relieved of the prolapse, developed partial incontinence of urine. This was ascribed to the surgeon's failure to form a high perineal body. The low perineal body produced undue traction on the internal vesical sphincter. Re-operation corrected the defect.

Four of the 38 followed-up patients died more than a year after the LeFort operation of unrelated causes—three of heart disease and one of carcinoma of the stomach.

Three of the 38 patients subsequently developed uterine hemorrhage, a phenomenon unrelated to the partial colpocleisis but dramatized by it because of the inaccessibility of the uterus for examination. The histories of these three patients, illustrating the management of uterine bleeding in women previously subjected to the LeFort operation, are herewith briefly outlined:

CASE 1.—Mrs. A. R., widow, aged 68 years, underwent a LeFort colpocleisis in September, 1937. She remained well for eighteen months, at which time metrorrhagia appeared. Not being able to perform either a diagnostic curettage or cervical inspection because of the partially closed vagina, we were forced to do an abdominal panhysterectomy in order to exclude the presence of carcinoma which, to our chagrin but great relief, was not present. The patient continued to be free from vaginal prolapse, but died of a coronary occlusion three years later.

CASE 2.—Mrs. S. L., widow, aged 53 years, had a LeFort colpocleisis in October, 1935, with an excellent result. Metrorrhagia appeared in March, 1944, at which time abdomino-rectal examination disclosed the uterus to be enlarged to that of a three months' gestation. Because the patient had previously received estrogen therapy for menopausal symptoms, the diagnosis of hematometra was entertained. Nevertheless, because carcinoma of the uterine fundus could in no way be excluded diagnostically, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed without disturbing the previous partial colpocleisis. The uterus contained an adenocarcinoma. Postoperative x-radiation was administered in the usual manner. When last examined, in March, 1947, the patient was free from symptoms, exempt from evidence of metastases, and without any degree of vaginal prolapse.

* CASE 3.—Mrs. E. Z., widow, aged 66 years, was subjected to LeFort colpocleisis, with excellent result, in July, 1940. Metrorrhagia appeared in February, 1947, but has not recurred since then. The patient is currently being regarded with "scientific apprehensive expectancy" and will be subjected to abdominal hysterectomy should the metrorrhagia recur. Papanicolaou vaginal smears are negative.

There is an obvious contraindication to the use of estrogen in women who had been previously subjected to partial colpocleisis, as illustrated in the histories just cited. If uterine bleeding occurs, there is no possibility of distinguishing benign, estrogen-evoked metrorrhagia from that caused by carcinoma. An abdominal hysterectomy must perforce be done. On the other hand,

CIRCULAR PROLAPSE OF THE URETHRA*

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PROLAPSE of the female urethra is a rare condition and although the volume of literature on the subject has increased considerably in recent years, most of it has come from Continental clinics. During the last half century, only twenty-two cases of prolapse of the female urethra have been reported in the United States, twelve by gynecologists and ten by urologists; almost one-half this number (9 cases) were reported in 1945.^{11, 16}

The following is a list of the cases reported in the United States.

TABLE I

| AUTHOR | CASES | AGES | YEAR REPORTED |
|----------------------------------|-------|-----------------------|---------------|
| Bagot ¹ | 1 | 50 | 1897 |
| Hepburn ⁴ | 2 | Adults, age not given | 1920 |
| Livermore ⁷ | 1 | | 1921 |
| Jacoby ⁵ | 1 | 63 | 1925 |
| Dannreuther ² | 1 | 7 | 1925 |
| Hepburn ⁴ | 1 | 54 | 1926 |
| Loux ⁸ | 1 | 5 | 1927 |
| Livermore ⁷ | 1 | 10 | 1927 |
| Ormond ¹² | 1 | 8 | 1931 |
| Keefe ⁶ | 1 | 53 | 1934 |
| Epsteen and Strauss ³ | 1 | 53 | 1935 |
| Mayer ⁹ | 1 | 60 | 1937 |
| Miller ¹¹ | 1 | 54 | 1938 |
| Zeigerman ¹⁶ | 4 | 49, 53, 57, 72 | 1945 |
| | 5 | 2, 43, 44, 57, 62 | 1945 |
| Total | 22 | | |

The literature in 1945 contained 311 collected cases¹⁶ as follows:

TABLE II

| AUTHOR | YEAR | NO. OF CASES |
|----------------------------------|-----------|--------------|
| Solingen ¹⁴ | 1732 | 1 |
| Sauferlin ¹⁵ | 1732-1926 | 270 |
| Epsteen and Strauss ³ | 1926-1937 | 300 |
| Zeigerman ¹⁶ | 1937-1945 | 311 |

Since 1945, eight additional cases were reported^{10, 11, 13} which, with the two herein described, make a total of 321 cases.

The lesion occurs at any age and is attended by tumor, pain, bleeding, and urinary complaints. The incidence is about 47 per cent in the age group of 5 days to 18 years; about 18 per cent between 18 to 45 years, and in women over

*Read at a meeting of the Philadelphia Obstetrical Society, Dec. 5, 1947.

Even in the worst type of prolapse, with little or no pelvic floor left to support a pessary, we have found that the ball-and-stem pessary slung from a belt around the waistline has given adequate support.

The fact that a number of different operative procedures for the correction of this condition are practiced by various clinics is adequate proof that there has been no single operation devised that completely meets the needs in all cases. In the final analysis, each case must be evaluated as to its individual requirements. The Fothergill-Manchester operation, with or without the Gilliam shortening of the round ligaments and shortening of the uterosacral ligaments, is probably the nearest approach to a perfect anatomic restoration to normalcy. When a short operative procedure is indicated, we favor the Watkin's interposition or the Fothergill shortening of the cardinal ligaments.

DR. ROBERT TAUBER.—In the last few years I have performed five LeFort operations with excellent results. There is no doubt that the operation has its field and cannot be replaced successfully in certain cases by any other surgical procedure. I described the modified technique which I used in my cases in detail in the *Annals of Surgery*, 125: 334, 1947.

DR. CLARENCE C. BRISCOE.—A patient on whom a LeFort operation had been performed bled following stilbestrol therapy which was prescribed despite the fact that she was some twenty-five years past the menopause. A pipette was inserted into each lateral gutter and the material obtained examined with the Papanicolaou stain. Bleeding stopped when stilbestrol was discontinued and subsequent Papanicolaou stains have been negative. It is suggested that the Papanicolaou stain may be useful in preventing unnecessary surgery in similar patients who have received estrogenic therapy.

DR. A. HERBERT MARBACH.—I would like to know more about the preoperative treatment of these patients. In ten colpocleisis cases done on our service we have had difficulty with two. These were early in the series and we felt that we were doing them on patients who were not adequately prepared for this type of surgery. At the present time we prepare our patients with large doses of Vitamin B complex, large doses of vitamin C, and prime the patient for a period of at least two weeks with stilbestrol, 5 mg. daily, until the time of operation.

I wonder if this is a factor. How does Dr. Israel feel about the preoperative treatment of these patients?

DR. GEORGE HAHN.—I had an experience two years ago with a patient who had had a vaginal hysterectomy, and the prolapse recurred. The vaginal wall was again brought together by means of a LeFort type colpocleisis, and no gutters left on either side because there was no cervix to produce vaginal drainage. So far the patient is well.

DR. ISRAEL (Closing).—Many of the opinions expressed are in consonance with the views of our paper. The question concerning cervical biopsy is proper. However, we must have been lucky, for none of the twelve cervixes we amputated were malignant. The question concerning the preoperative preparation of these patients requires emphasis. Each of these patients had at least five days, more commonly a full week, of preoperative preparation which included daily cleansing of the vagina with some mild antiseptic solution and the maintenance of the prolapsed organs in good position. The suggestion of following the post-LeFort patient who shows bleeding, presumably from the hidden uterus, by vaginal smears is a good one. It could well be that this cytological technique would aid the puzzled gynecologist in his decision to perform abdominal hysterectomy.

DR. MAZER (Closing).—Dr. Leff refers to the type of genital prolapse wherein the Fothergill or the interposition operation may be employed successfully. However, when the genital prolapse is complete, as seen in some elderly women, or when the vagina is completely prolapsed following a hysterectomy, neither the Fothergill nor the interposition operation can do any good. In such cases the LeFort operation is indicated, if marital relationship is no longer a factor.

CASE 2.—No. 75187, Pennsylvania Hospital. Admitted April 20, 1946, discharged, April 27, 1946.

D. W., a 9-year-old white girl was admitted with pain, vaginal bleeding, and discomfort on urination. She had had recurrent attacks of spotting of blood from infancy until she was five years old. Six weeks prior to admission, she fell from a bicycle and had bleeding from the vagina for two weeks. Vaginal inspection revealed a tumor mass which was thought to be a traumatic injury of the anterior vaginal wall protruding through the hymenal ring. On subsequent examinations, the lesion proved to be a circular prolapse of the urethral mucosa. After application of compresses and bed rest for two weeks, the lesion was excised by circumcision. Silver wire sutures No. 36 were placed about the urethral orifice; one anteriorly, one posteriorly, and one on either side as a guide in subsequent resection. The excess mucosa was excised in quadrants to the level of the silver wire and the cut edges were approximated with fine catgut. The silver wires were then removed. A Foley catheter remained in the bladder for four days. The convalescence was uneventful and the patient was discharged in good condition. A re-examination nine months later showed no recurrence of the prolapse.

Altogether seven cases of urethral prolapse had been treated by us over a period of eight years with good results. The following is a résumé of age, symptomatology, duration of symptoms, precipitating causes, and the results of the operation, in each of our cases.

TABLE III. ANALYSIS OF THE INDIVIDUAL CASES

| AGE | ACUTE SYMPTOMS | DURATION OF ACUTE SYMPTOMS | DURATION OF CHRONIC SYMPTOMS | PRECIPITATING CAUSE | |
|-----|---|----------------------------|--|---------------------|----------------------|
| | | | | DIRECT | INDIRECT |
| 2 | Vaginal bleeding Painful lump in vagina Painful urination | 1 week | ----- | ----- | Persistent cough. |
| 9 | Vaginal bleeding Painful lump in vagina Painful urination | 1 week | ----- | Kicked in vulva | ----- |
| 62 | Vaginal bleeding Painful lump in vagina Painful urination | 1 week | ----- | ----- | Chronic constipation |
| 9 | Vaginal bleeding Painful lump in vagina Painful urination | 2 weeks | Recurrent vaginal staining for 5 years. | Fell off bicycle. | ----- |
| 57 | Vaginal bleeding Painful lump in vagina Painful urination | 1 day | Lump in vagina without symptoms several years. | Unknown | Unknown |
| 43 | Vaginal bleeding Painful lump in vagina Painful urination | 4 days | Lump in vagina without symptoms for 4 years. | ----- | Diarrhea |
| 44 | Vaginal bleeding Painful lump in vagina Painful urination | 1 week | Intermittent symptoms 3 years. | ----- | Cystitis |

The onset, as observed in the majority of cases herein reported, points to a pre-existing lesion of the urethra with minimal symptoms for several years, followed by direct or indirect trauma, which produced the acute symptoms.

Direct trauma was the precipitating cause in the two nine-year-old girls, an abnormal increase in intraabdominal pressure due to persistent cough, chronic constipation, and diarrhea in three other patients, and a subacute cystitis of long standing in the sixth case.

45 years, about 35 per cent. The greatest incidence is between 8 and 12 years of age and 60 to 65 years. The youngest patient whose case was reported was a child 5 days old, and the oldest a woman of 92 years.

The symptoms and size vary with the extent of the circulatory disturbance. There may be necrosis and even gangrene of the prolapsed mass. The urethral orifice may be difficult to find as it often deviates to one side of the tumor mass, even necessitating in some cases a general anesthetic to disclose it. A biopsied specimen usually shows acute or chronic inflammation, engorgement, thrombosis, and, occasionally, hypertrophied submucous glands. The muscle layer is usually absent.

The histories of the two patients seen by us recently are briefly recorded here.

CASE 1.—No. 175561, Graduate Hospital, University of Pennsylvania. Admitted, Dec. 17, 1946, discharged, Jan. 20, 1947.

J. J., 9-year-old Negro girl, admitted with vaginal bleeding, painful urination, and a painful lump in the vagina. The child was in perfectly good health until one week ago, when she was kicked in the vulva by her 2-year-old sister. Following the injury, there was a small amount of bleeding and pain in the vagina; this had continued every day since the injury.



Fig. 1.—Circular prolapse of the urethral mucosa protruding from the vaginal introitus in a 9-year-old girl.

Vaginal inspection revealed a red fleshy mass protruding from the vagina and filling the introitus. This mass was first thought to be a hematoma of the right rim of the external urinary meatus due to trauma. Under general anesthesia, the prolapsed urethra was exposed and a catheter introduced into the meatus, confirming the diagnosis of circular prolapse of the urethral mucosa. She was confined to bed and after application of compresses and bed rest for three weeks, the lesion was excised by circumcision. Chromic O sutures were placed about the urethral orifice, one anteriorly, one posteriorly, and one on either side as a guide in subsequent resection. The excess mucosa was then excised in quadrants to the level of the catgut and approximated with two additional interrupted sutures of fine catgut placed between the original quadrant sutures. A Foley catheter remained in the bladder for three days. The convalescence was uneventful. Studies of the bladder and renal function revealed no abnormality. A re-examination eight months later showed no recurrence of the prolapse and the patient had no complaints.

TABLE III. FOLLOW-UP REPORT

| AGE | DIAGNOSIS | OPERATION | YEAR | RESULTS |
|-----|-------------------|--------------|------|---------------|
| 43 | Circular prolapse | Circumcision | 1939 | No recurrence |
| 62 | Circular prolapse | Circumcision | 1940 | No recurrence |
| 57 | Circular prolapse | Circumcision | 1942 | No recurrence |
| 2 | Circular prolapse | Circumcision | 1944 | No recurrence |
| 9 | Circular prolapse | Circumcision | 1946 | No recurrence |
| 9 | Circular prolapse | Circumcision | 1946 | No recurrence |

Summary and Conclusions

1. 321 cases of urethral prolapse have been reported in the world literature.
2. Only 22 cases were reported in this country during the past 50 years.
3. The onset is gradual and may continue over many years.
4. The circumcision operation is adequate for the treatment of prolapse of the urethra.
5. The excision of the mucosa in quadrants diminishes bleeding, gives better approximation of tissue, and serves as a guide in resection.

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Treatment

The seven cases seen by us were treated by excision of the prolapsed mucosa and suturing the cut edges.

The technique of resection used in the last two cases has greatly simplified this operation. The suture ligatures which were placed at 3, 6, and 9 o'clock on the face of the prolapse at the mucocutaneous junction served as a guide in the subsequent resection, preventing the retraction of the mucosa and diminishing the loss of blood.

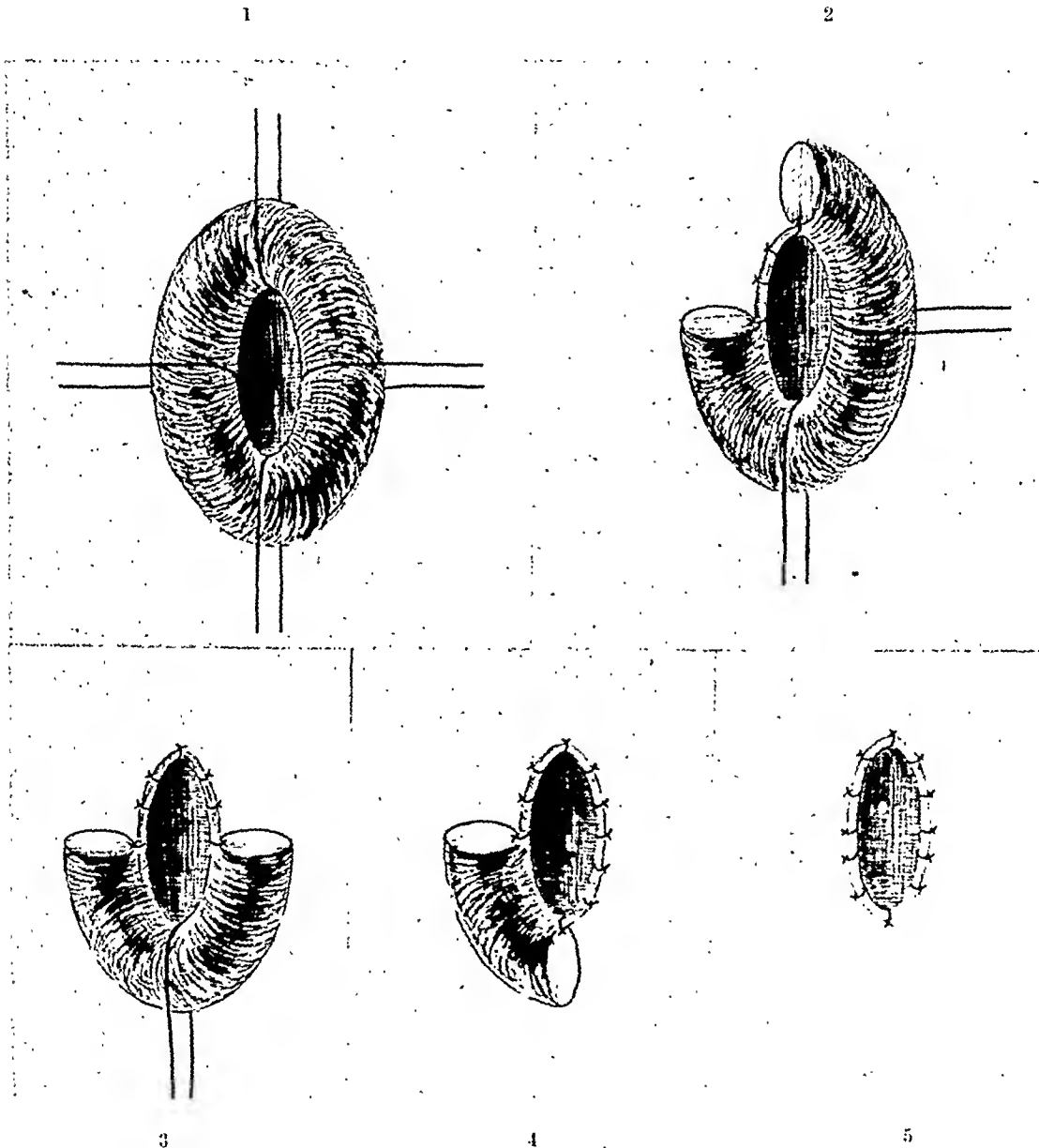


Fig. 2.—Resection of the circular prolapse in quadrants. Guide sutures tied. Single sutures added. 1. Showing guide sutures. 2. First quadrant removed. Guide sutures tied. Single sutures added. 3. Second quadrant removed. Single sutures added. 4. Third quadrant removed. Single sutures added. 5. Fourth quadrant removed. Single sutures added.

In our experience with this condition, it was found that simple excision of the prolapsed mucosa has given excellent results; in none of these cases was there any recurrence.

4. *Detection of Histidine.*—The clear test solution is brominated as in Knoop's method.¹ A reagent of bromine in 33 per cent acetic acid is employed, and an excess of bromine is maintained in the mixture for about ten minutes. One-half cubic centimeter of an ammonium carbonate reagent (3 per cent ammonium carbonate in 2:1 ammonium hydroxide) is then added and the mixture heated at about 95° C. for several minutes. If sufficient histidine is present, a red-purple or bright pink color develops which fades upon standing.

Results of the Chemical Pregnancy Test

More than 400 determinations were made by the Carson-Saeks chemical procedure for histidinuria. All specimens were obtained from the practice of the senior author, and results were verified clinically by him. Tests were performed by Carson and Sacks.* Not all specimens were controlled as to diet, time of collection, etc. The results, shown in Table I, indicate an accuracy of 95.1 per cent in clinically positive cases and 92.6 in clinically negative cases. In Table II is presented a tabulation of results as correlated to the time of last menstruation prior to collection of the specimen. Eight male urines were tested to afford an additional check on the specificity of the reaction.

TABLE I. SUMMARY OF CLINICAL DATA OBTAINED FROM TESTS BY CARSON-SAEKS METHOD

| CLINICAL FINDING | NO. OF CASES | NUMBER | | PER CENT | |
|------------------|--------------|---------|-----------|----------|-----------|
| | | CORRECT | INCORRECT | CORRECT | INCORRECT |
| Positive | 268 | 255 | 13 | 95.1 | 4.9 |
| Negative | 163 | 151 | 12 | 92.6 | 7.4 |
| Total | 431 | 406 | 25 | 94.2 | 5.8 |

TABLE II. SUMMARY OF DATA CORRELATED WITH DATE OF CESSATION OF MENSTRUATION

| PERIOD SPECIMEN TAKEN | POSITIVE | | | | NEGATIVE | | | | TOTALS | | | |
|--------------------------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|
| | NUMBER | | PER CENT | | NUMBER | | PER CENT | | NUMBER | | PER CENT | |
| | COR-RECT | INCOR-RECT | COR-RECT | INCOR-RECT | COR-RECT | INCOR-RECT | COR-RECT | INCOR-RECT | COR-RECT | INCOR-RECT | COR-RECT | INCOR-RECT |
| First month | 24 | 2 | 92.5 | 7.5 | 30 | 1 | 96.7 | 3.3 | 54 | 3 | 94.7 | 5.3 |
| Second month | 68 | 1 | 98.7 | 1.3 | 7 | 3 | 70.0 | 30.0 | 75 | 4 | 94.9 | 5.1 |
| Third month | 56 | - | 100 | - | - | 4 | - | 100 | 56 | 4 | 93.3 | 6.7 |
| Fourth month | 35 | 1 | 97.4 | 2.8 | - | - | - | - | 35 | 1 | 97.2 | 2.8 |
| Fifth month | 13 | - | 100 | - | 1 | - | 100 | - | 14 | - | 100 | - |
| Sixth month | 2 | - | 100 | - | 1 | 1 | 50 | 50 | 3 | 1 | 75 | 25 |
| Seventh month | 3 | - | 100 | - | - | - | - | - | 3 | - | 100 | - |
| Eighth month | 1 | - | 100 | - | - | 1 | - | 100 | 1 | 1 | 50 | 50 |
| Last menstrua- tion unknown | 30 | 6 | 83.3 | 3.7 | 91 | 1 | 98.9 | 1.1 | 121 | 7 | 94.5 | 5.5 |
| Postpartum | - | 1 | - | 100 | 20 | - | 100 | - | 20 | 1 | 95.2 | 4.8 |
| Male urine | - | - | - | - | 8 | - | 100 | - | 8 | - | 100 | - |
| Totals | 232 | 11 | 94.7 | 5.3 | 158 | 11 | 93.6 | 6.4 | 390 | 22 | 94.4 | 5.6 |

For the sake of comparison, the accuracy of this test is compared with that of other methods of diagnosis. The chemical test of Voge,² modified by Kapeller-Adler,^{3, 4} is based on the finding of histidinuria, as is our test. The test of Visscher-Bowman⁵ is based on the reducing properties of gonadotropin. The Guterman test⁶ depends on a color reaction of urinary pregnandiol. The criticism has been voiced⁷ that (1) the concentration of pregnandiol in early pregnancy is too low to make it of value as an early diagnostic test, and (2) the incidence of false positive reactions is high in cases of delayed menstruation. The standard

*We are indebted to Westerfield Pharmacal Co., Inc., for their assistance and supplies of materials.

A CHEMICAL TEST FOR PREGNANCY

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THE early diagnosis of pregnancy, always a matter of wide interest in obstetric practice, has become more important than ever, since we have learned so much about its physiologic implications. As a consequence of early diagnosis, it becomes possible better to advise the patient with respect to hygienic, psychic, dietary, and other adjustments to pregnancy. It permits us to apply safeguards to protect mother and child against possible adverse effects resulting from endocrine or other disturbances, or from an unpropitious Rh relationship.

A simple, rapid, and reliable office test has been developed by two of the authors (Carson and Sacks), and used in collaboration with the senior author in over 400 cases.

The test is based on the established finding that during normal pregnancy, histidine is excreted in substantial amounts. This knowledge has been used before in diagnostic procedures, but earlier tests have had the disadvantages of either overwhelming unwieldiness or insufficient accuracy.

Essentially, the test consists of the following steps: (1) control of specimen, (2) dilution, (3) removal of substances which interfere with the test, and (4) detection of histidine by Knoop's Method. One or more tests can be run in a period of twenty to thirty minutes.

1. *Control of Specimen.*—It has been observed by the authors and others that after a heavy intake of protein, the urine of a nonpregnant woman may show histidine, but in relatively small amounts. They have found that if reliable results are to be obtained with a histidine test, there should be at least one urination after the ingestion of food before the specimen is taken. An early morning specimen is preferable. It has also been observed that histidine is frequently present in the urine during menstruation as well as two to three days before the onset of the flow. Therefore, it would seem inadvisable to use a specimen taken near the end of the menstrual cycle because of the likelihood of obtaining false positive results.

2. *Dilution.*—It is often possible to detect histidine in specimens of high specific gravity. For the purpose of avoiding the possibility of the test showing histidine in the urine of a nonpregnant woman, we prepare the specimen by diluting it to a concentration so low that the small amount of histidine which might occur in urine in such an instance will not be indicated by the test. The amount by which the urine is to be diluted is determined by both its specific gravity and pH. By experiment, we have found that an alkaline specimen should be diluted with water to a specific gravity of 1.009, and an acid specimen should be diluted to a specific gravity of 1.005.

3. *Removal of Interfering Substances.*—A 5 c.c. portion of the diluted specimen is used for making the test. Phosphates are precipitated with a 10 per cent barium chloride solution. Nitrites are oxidized with 0.1 N potassium permanganate reagent. Solids are removed by filtration.

Summary

A new chemical test for pregnancy is proposed. The test depends upon a modified procedure for the estimation of histidine excretion in pregnancy. The physiologic basis of the test is discussed. Studies on more than 400 cases indicate that the method is rapid, simple, and accurate enough to justify its use, particularly as an office procedure.

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biological tests (Aschheim-Zondek and Friedman) are, of course, highly accurate; however they are not suitable for use as office procedures.

Table III presents a comparison of some of the tests used in the early diagnosis of pregnancy with the Carson-Sacks method.

TABLE III. COMPARISON OF TESTS FOR EARLY DIAGNOSIS OF PREGNANCY

| | CASES | CLINICAL POSITIVES | CLINICAL NEGATIVES |
|--|--|--------------------|--------------------|
| | | RANGE OF ACCURACY | RANGE OF ACCURACY |
| <i>Chemical tests</i> | | | |
| <i>Histidinuria</i> | | | |
| Carson-Sacks Test | 412 | 94.7% | 94.4% |
| Voge and Kapeller-Adler (reviewed by Mello ⁸) | 2,350 | 63%-95.2% | 75%-98% |
| Visscher-Bowman Test (revised by Mello ⁸) | 961 | 66%-100% | |
| <i>Biological tests</i> | | | |
| Aschheim-Zondek (cited by Weisman ⁹) | 2,807 | 94% | 97% |
| Friedman Test | About the same as Aschheim-Zondek test | | |

Discussion

The histidine excretion test for the early diagnosis of pregnancy is based on established findings that histidine metabolism is significantly altered during pregnancy. Normally, histidine is converted by the liver into histamine.¹⁰ However, during pregnancy, it is excreted in the urine, possibly because of the effect of prolactin on the ability of the liver to inactivate histidine,³ or a lowering of the renal threshold for histidine in the pregnant woman.¹¹

The histidine test for pregnancy has been in use for about fifteen years; previous results have been variable for two principal reasons. (a) The diet of the patient in regard to protein intake was not controlled prior to collection of the specimen; and (b) tests were performed on concentrated urines which reduced sensitivity and specificity of the test.

Certain pathologic conditions may lead to false results. When pregnancy is complicated by eclampsia, histidine disappears from the urine.¹² Endocrine disturbances (thyroid, pituitary, or adrenal) may interfere with the specificity of the test.^{11, 13} Urinary excretion of amino acid may occur in persons with extensively impaired hepatic function or those exhibiting severe tissue autolysis.¹⁴ The existence of nutritional deficiencies may cause a weak positive or false negative reaction in pregnant individuals.

While these factors appear to be detrimental to the accuracy of the test, it may be considered that false reactions may serve as a guide to further study of the patient with a view to possible diagnosis of endocrine or other disturbance. Studies are now in progress to extend our knowledge of the significance of false findings.

It must be noted that not all the urine specimens were obtained under optimal conditions. One might expect a greater degree of accuracy if care were taken to assure in every case that (1) the specimen was obtained early in the morning or several hours after ingestion of a protein-rich meal; and (2) the patient had voided urine after such a meal before the specimen is collected.

Since the areas of intervillous thrombosis are usually composed of well-preserved cells, it seemed possible to settle the problem of their origin by typing the blood of the mother, infant, and thrombus.

During 1944, 1660 placentas delivered from patients at the Chicago Lying-in Hospital were examined. These were not all delivered consecutively but during the periods of study the placentas of all patients were investigated.

The lesions described above are almost never visible on the external surface of the placenta and are found only in the central portions of the cotyledons. Consequently all placentas were placed on a board and the substance was cut with a long knife into slices approximately 1 cm. thick.

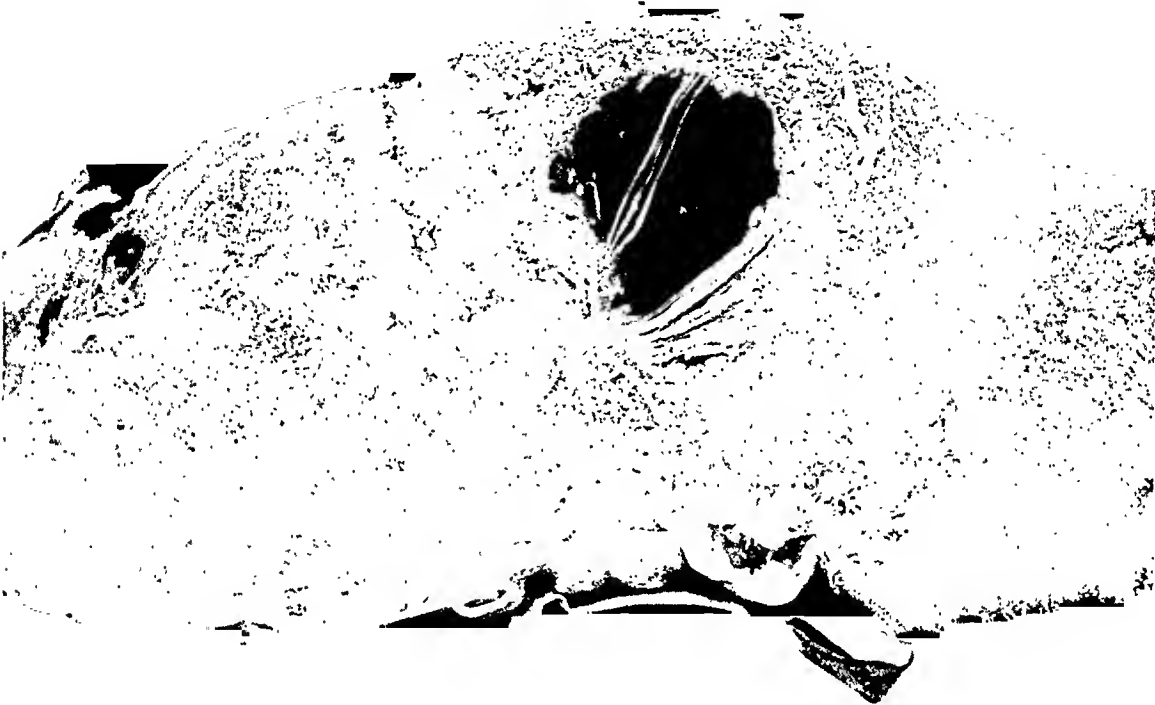


Fig. 1. Portion of placenta containing an area of intervillous thrombosis.

Among the 1660 placentas that were examined, thrombi were found in 60, an incidence of 3.6 per cent. Of these, only 4 were too old to permit typing the cells. The results of typing the blood of the mother, the blood of the umbilical cord, and the cells of the thrombus in the remaining 56 are shown in Table I.

TABLE I. RELATION OF THE BLOOD GROUP OF CELLS IN PLACENTAL THROMBI TO THE BLOOD GROUPS OF MOTHER AND INFANT

| NUMBER | THROMBUS | INFANT | MOTHER |
|--------|----------|--------|--------|
| 22 | O | O | O |
| 20 | A | A | A |
| 2 | B | B | B |
| 5 | A | O | A |
| 2 | B | A | B |
| 2 | O | B | O |
| 2 | A | B | A |
| 1 | O | A | O |

INTERVILLOUS THROMBI IN THE PLACENTA AND THEIR POSSIBLE RELATION TO ERYTHROBLASTOSIS FETALIS

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WITHIN the central part of a cotyledon in an occasional placenta is found a red laminated area measuring from a few millimeters to slightly over 2 cm. in diameter. These structures are somewhat irregular in shape but they usually assume a fairly round or cuboidal form. The neighboring villi are pushed back and none are present within the lesion. (Fig. 1.) Occasionally surrounding the central area is a peripheral zone of degenerated villi measuring 3 to 10 mm. in diameter caused by compression with a secondary degeneration due to local absence of maternal blood.

These areas have been often classed as infarcts but are better considered as thromboses since their structure is similar to that of a thrombus. The color depends on the length of time they have been present but the majority are dark red and are streaked with light yellow lamina due to local deposits of fibrin and platelets. They seem to occur ordinarily only late in pregnancy for similar structures in which blood cells have been destroyed and which are consequently yellow are uncommon.

Such thrombotic areas have generally been considered of maternal origin but the statement has been made on several occasions that they are of fetal origin and Javert¹ believed their presence proved that fetal blood might leak out of the vessels in the villi into the maternal circulation. He gave as proof the fact that nucleated red blood cells were thought to have been found in such areas in the placentas of infants with erythroblastosis. This statement has been widely quoted as evidence that escape of fetal blood into the maternal circulation does occur and that it may be the means of producing maternal immunization when the mother is Rh negative and the fetus is Rh positive.

The same author has further stated that retroplacental hematomas are evidence of hemorrhagic disease of the fetus and that the administration of vitamin K before the expected onset of labor should be of benefit in preventing premature detachment of the placenta.

The present study was undertaken in an attempt to determine whether these areas of intervillous thrombosis are actually composed of fetal blood or whether the cells are of maternal origin. Leucocytes are frequently found in large masses in any thrombus, due to the layering which results from the manner of deposition, and it is possible that the nuclei of lymphocytes might have been mistaken for those of immature red blood cells.

EXTRAUTERINE PREGNANCY AT TERM WITH DELIVERY OF A NORMAL LIVING CHILD AND LIVING MOTHER*

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ABDOMINAL pregnancy is a condition which is seldom, if ever, met with in a lifetime practice of obstetrics. When encountered, however, it presents a most difficult problem to the obstetrician as to management and is accompanied by an extremely high mortality to mother and child. In a review of the literature on this subject, Cornell and Lash in 1933 reported two hundred thirty-six cases of abdominal pregnancy, with a maternal mortality of 14.3 per cent. In eighty-six cases where the baby was born after the sixth month of pregnancy, there was an infant mortality of 22 per cent, while in sixty cases where the baby was born alive in the eighth or ninth month of pregnancy, the mortality was 35 per cent. In 1935, Hellman and Simon reported three hundred sixteen cases of abdominal pregnancy, in which the mother survived in two hundred twelve cases and the fetus in one hundred fifty-eight cases. In eighty cases, both mother and child survived—that is, lived eight days or longer. Woods reported a case of abdominal pregnancy with a normal living baby but the mother died within a few days after delivery from an overwhelming toxemia as a result of peritonitis. In November, 1944, Gardner reported a case in which both mother and baby survived, and the latter, weighing four pounds and fifteen ounces, was without congenital defects or anomalies. This infant died at four and one-half months, however, from pneumonia, and the mother expired two years later from a metastasizing carcinoma of the breast. Beacham, in a review of abdominal pregnancy, cites numerous instances throughout the literature where both mother and child survived. However, in a great majority of instances where the fetus was alive at birth, a neonatal death ensued in a matter of hours or days after delivery, and many of the infants showed single or multiple congenital defects.

It is, therefore, still a rarity to deliver a normal living baby free of congenital defects and to be fortunate enough to secure a satisfactory maternal result as well. Such a case was encountered at Temple University Hospital, Philadelphia, over a year ago.

Case Report

The patient was a twenty-one-year-old Negro primigravida who presented herself at the out-patient department of Temple University Hospital approximately five months pregnant. Her history was as follows:

The patient's last menstrual period was Sept. 17, 1944. On Oct. 15, 1944, there was an episode of vaginal bleeding which lasted for two days. The flow was intermittent in character and very scanty. There were no further complaints until Dec. 23, 1944, when, after a fall in her home, apparently without abdominal trauma, the patient experienced considerable abdominal pain and complained of weakness. Since pain was more or less constant and aggravated by motion, the patient remained in bed for one week. At the end of this period, she felt no better and consulted her family physician who hospitalized her at another institution for a seventeen-day period at complete bed-rest. During this time, she continually improved, although there was still slight lower abdominal distress at times. Because of the continuation of these symptoms, she registered at the out-patient department of Temple University Hospital in the latter part of February, 1945.

On her first visit, examination revealed abdominal enlargement compatible with five months' gestation. Although there was considerable abdominal tenderness and pelvic examina-

*Presented at a regular meeting of the Philadelphia Obstetrical Society.

In 44 of the 56 thrombotic areas in which the cells were satisfactorily typed, the mother, thrombus, and infant were of the same blood group. Among the 12 in which the mother and infant were of different blood groups, all of the thrombi without exception were of the same group as the mother and none were of the same group as the infant.

If, in this large a group of placentas, there were no infarets composed of fetal blood, it seems reasonable to conclude that such infarets either do not exist or do so with the greatest rarity. It is the author's belief that such infarets are always of maternal origin and are unrelated to the possible etiology of erythroblastosis fetalis or hemorrhagic disease of the newborn. Consequently, the citation of the presence of such thrombotic areas as proof that fetal cells may escape from the vessels in the villi, and so escaping may be the source of maternal immunization to the Rh factor does not seem justified. The fact that these areas are not composed of fetal cells does not prove that fetal cells may not enter the maternal circulation from the villi, but if proof for such intermixture of cells is desired it must be obtained by others means.

Summary

Examination of 1660 placentas revealed the presence of intervillous thrombosis in 3.6 per cent. Among 56 placentas in which the cells of the thrombi could be typed the blood groups of the infant, mother, and thrombus were the same in 44. In the remaining 12, in which the mother and the infant belonged to different blood groups, the cells of the thrombus were in all instances of the same type as those of the mother. The presence of such thrombi cannot be used as proof for the contention that fetal blood may escape from the villi during pregnancy and may consequently be the cause of maternal immunization when the fetus is Rh positive and the mother is Rh negative.

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Roentgenologic report at this time read as follows:

"An intrauterine pregnancy with fetus at term lying in left occiput anterior position, vertex almost engaged. The pelvis seems ample for vaginal delivery. The placenta is situated high up in the upper segment of the uterus slightly to the left and posteriorly." (Fig. 1.)

After seventy-two hours of hospitalization, all the patient's symptoms disappeared and she was discharged. On July 26, 1945, patient was again admitted for twenty-four hours but was discharged as in "false labor." There was no bleeding on this admission.

On Sept. 2, 1945, patient was seized with severe colicky-type abdominal pain. There was again a slight bloody discharge. The pains increased in severity and frequency until twelve o'clock midnight, when patient stated they took her breath away. She was admitted to the hospital and examination revealed the patient in acute distress. Temperature 98°; pulse 95; respiration 22; blood pressure 118/72. In spite of these findings, she gave one the impression of shock. The abdomen was tense, extremely tender, slightly distended and peristalsis was absent. The mass noted formerly was acutely tender. The fetus seemed at term with back to the left in left occiput anterior position, head was thought to be engaged at plus one station and there was no cervical dilatation. Fetal heart tones were not audible. Admission blood count was: Red blood count, 4.65; hemoglobin, 12 Gm.; white blood count, 11,900. The urinalysis report was entirely negative. A diagnosis was made of placenta abruptio (partial) with the possibility of ruptured appendix and degenerating fibroid. It was decided that abdominal exploration was indicated.

Operative Findings.—On opening of the peritoneal cavity, a greenish-yellow exudate was encountered (subsequent culture report showed no growth), and there were about 300 to 500 c.c. of free peritoneal fluid. The appendix was normal. The uterus was noted in the midline just above the symphysis enlarged to twice normal size. The right tube and ovary were normal. The left ovary could not be visualized and the left tube was lost in the wall of a large mass which lay just to the left, and beneath the uterine body and extended from deep in the pelvis to a point just under the diaphragm. This mass seemed entirely retroperitoneal. The small bowel, sigmoid, and cecum were covered with a greenish-yellow exudate and were slightly injected, although in no way adherent to the mass. The omentum was adherent to the upper portion of the mass and large vessels were springing from this point which anastomosed over the surface of the mass with other large vessels which seemed to be springing from the mesentery of the small intestine.

An incision was made in the lower portion of the mass in the region of the left broad ligament since this area was relatively avascular. Considerable greenish-yellow exudate was encountered which was the same as that noted in the peritoneal cavity, indicating that there must have been a perforation of the sac before delivery. An eight-pound, two-ounce female fetus was extracted by breech. The infant was living, breathed readily and appeared to be entirely normal. Exploration of the sac revealed the placenta in the upper portion slightly to the left and posteriorly situated. A chromic No. 2 catgut double ligature was placed around the cord close to the placental attachment and a large Babcock sump was placed in the bed of the sac, after which the sac was closed with no attempt made to remove the placenta. Another sump drain was inserted in the right iliac fossa.

Postoperative Course.—The patient did well the first three days postoperatively. On the third day, the temperature was normal and the abdomen flat with active peristalsis. Drainage was slight and the sump drain to the right iliac fossa was removed. In this early postoperative period, the patient received parenteral fluids freely with 500 c.c. whole blood and sodium sulfadiazine, 2 Gm. every six hours intravenously for the first forty-eight hours. On the third day, penicillin was started, giving twenty thousand units every three hours and this was continued until a total of four million three hundred ten thousand units had been administered. From the third postoperative day, the patient ran a temperature of 101° F. to 102° F. for the next eight weeks. On the tenth postoperative day, the sump drain within the amniotic sac was removed and a large rubber catheter inserted. On the twelfth day, it was felt that an abscess was forming in the right lower quadrant area but on opening the abdomen in this site, nothing but indurated tissue was found, and no drainage was obtained. The patient drained

EXTRAUTERINE PREGNANCY

tion difficult, it was noted that the cervix was soft and the uterus seemed enlarged to the size of a five months' pregnancy. Pelvimetry was adequate and the remainder of her physical examination was negative.

She was examined thereafter at three-week intervals. Pregnancy progressed and fetal heart sounds became audible on second clinic visit; patient noted fetal movement at this time. On her third visit, a mass was noted in midline just above the symphysis, which was thought to be a small fibromyoma. The abdominal distress continued but did not increase in severity.



Fig. 1.—Roentgenogram taken two weeks before term.

Pregnancy continued until July 6, 1945, when the patient was hospitalized because of spotting and accentuation of her lower abdominal distress which she thought was labor. Examination showed abdominal enlargement compatible with a full-term pregnancy. There was a mass noted in midline just above the symphysis which was approximately six to eight centimeters in diameter. It was extremely tender on palpation. Fetal heart sounds were readily audible in the left lower quadrant. The position was diagnosed as left occiput anterior. Rectal examination revealed vertex at minus one station in the pelvis.

MESODERMAL MIXED TUMORS OF THE UTERUS

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TUMORS composed of a variety of tissues are not uncommon in many locations in the body, such as mixed tumors of the salivary glands and embryonal sarcomas of the urinary tract. However, mesodermal mixed tumors of the uterus are rare, only ninety-four having been reported up to 1941, and in more recent years several comprehensive reviews of mesodermal mixed tumors have appeared.^{2, 5-12} The first of these tumors was described by Wagner in 1854. Recently, two tumors which appear to be mesodermal mixed tumors of the uterus were encountered in this hospital: one was a small myxomatous cervical growth, and the second a large, bulky, widely extended tumor of the fundus.

CASE 1.—A 22-year-old, white, single, nulliparous woman when first seen was complaining of irregular menstrual periods with a somewhat increased flow for the past six months. Prior to this she had had no menstrual irregularity. Lately, the periods occurred every twenty-eight to thirty-five days with four to seven days of bleeding at each time, and the flow had been moderately profuse. On several occasions during the past three months, she had slight intermittent intermenstrual spotting. The urinalysis was normal and the blood count was hemoglobin 15 Gm. per 100 c.c., red blood cells 4,800,000, white blood cells 8,600, coagulation time three minutes. The Kline and Wassermann tests were negative. Vaginal examination revealed a round nodule approximately 1 cm. in diameter, which was firm and superficially lobulated. The attachment to the anterior lateral portion of the cervix was nearly the width of the tumor. The epithelium covering the tumor was less pink than the surrounding epithelium, and there were small superficial blood vessels over the surface. At operation, the base of the tumor mass was removed with a wide excision. The cervix was dilated and the uterine cavity curetted with a moderate yield of endometrium.

The block of cervix measured 8 by 10 by 25 mm. Part of the epithelial surface was smooth and glistening. Projecting above this uniform surface for approximately 3 mm. was a circular area 1 cm. in diameter which appeared to be composed of small rounded projections somewhat like a miniature bunch of grapes. The cut surface below this roughly granular area was firm and had a light gray homogeneous appearance.

Microscopic examination of the cervical biopsy disclosed a peculiar myxomatous infiltration beneath the cervical epithelium. This growth was seen invading the connective tissue of the cervix in all directions, and was even invading into and around the glands. It had broken through the surface epithelium in several areas, forming small papillomas in one location. The stroma was a fibrillary semimyxomatous material which extended into the fibrous elements of the cervix and separated them in many places. The normal cervical structures were completely replaced by the tumor over areas as large as a low-power field. The most prevalent cell was a large cell with long processes extending in several directions. Some were star shaped with four or five long arms extending through the stroma; others appeared to have only one or two long arms. These cytoplasmic elongations were occasionally three to four times the diameter of the body of the cell, and could be seen best in the phosphotungstic acid hematoxylin stained preparations. Those from cells in the same field often interlaced, forming a loose network. The myxomatous stroma did not stain for mucin, but in slides stained by the Masson method it appeared to be composed of very minute granules arranged in long strands interlacing at many points so as to form a fine network. A few cells were roughly oval with one end flattened. In these cells the nucleus was in midposition,

continually, at some times a frankly bloody drainage and on other occasions, a brownish purulent material, cultures of which showed throat-type anaerobic nonhemolytic streptococci. There was never any evidence of pointing or abscess formation in the pelvis thereafter which would be suitable for colpotomy or abdominal drainage. There was a marked anorexia for five or six weeks and considerable weight loss. A rather severe anemia developed which responded well to small frequent blood transfusions. The total period of drainage was two months. The total period of hospitalization was one hundred one days.

Follow-Up Visits.—The abdominal incisions were well healed and pelvic examination was normal except for considerable induration just to the left of the uterus, with adhesive bands from this point to the abdominal scar. The baby gained well, weighing fifteen pounds at five months.

At the end of a year, the child was walking and the mother seemed no worse for her experience. There still remained some induration in the left adnexal area, but no tenderness and no particular complaints.

It is interesting to note that the patient carried this pregnancy almost a year according to her menstrual history. That death of the fetus did not occur seems remarkable. Also interesting is the attachment site of the placenta, which, in this case, was high in the sac, while in most cases of this kind, attachment is usually lower and against the uterus.

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1420 WEST ERIE AVENUE.

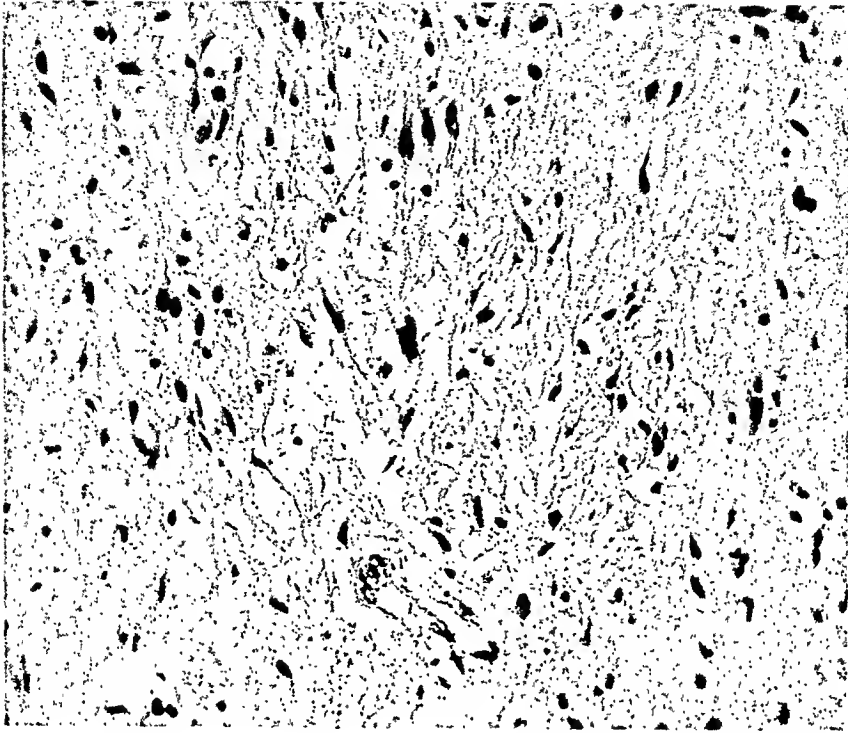


Fig. 2.—Case 1. Stromal elements showing elongated cytoplasmic processes and occasional giant cells.

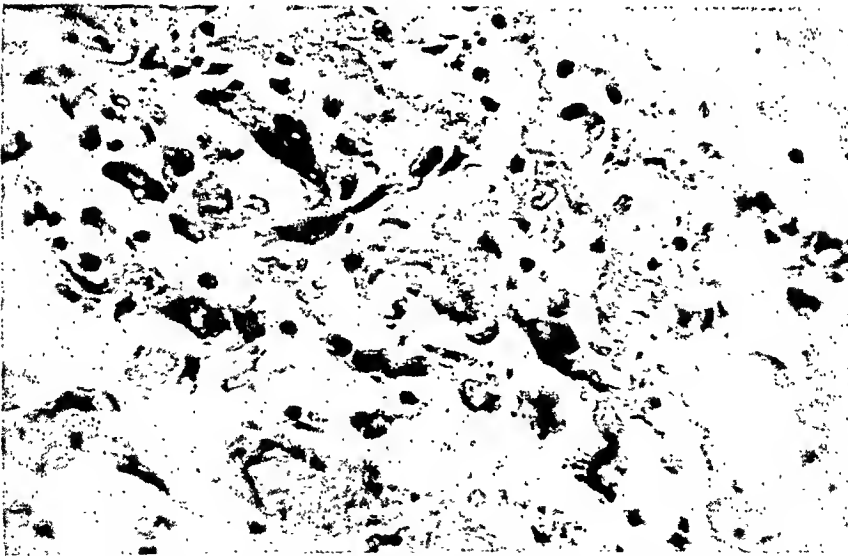


Fig. 3.—Case 1. An area with several multinucleated cells, the cytoplasm of the large cell in the upper left hand portion has darkly staining areas suggesting early cross striations.

usually filling the breadth of the cell. The cytoplasm was clear except for small dark granules which occasionally appeared to be arranged in lines or rows near the ends of the cells. A few multinucleated giant cells were present, some of which had two to five nuclei along the periphery of the cell, as can be seen in primitive striated muscle cells. Several giant cells had vague cross striation which suggested myoblasts, but striated muscle was not demonstrated although special stains were performed. Other giant cells had a clear cytoplasm, usually with two nuclei in the central portion. It was felt that this constituted a malignant invasive tumor which extended beyond the edges of the biopsy and which would probably be radioresistant. Therefore, a complete hysterectomy was advised.

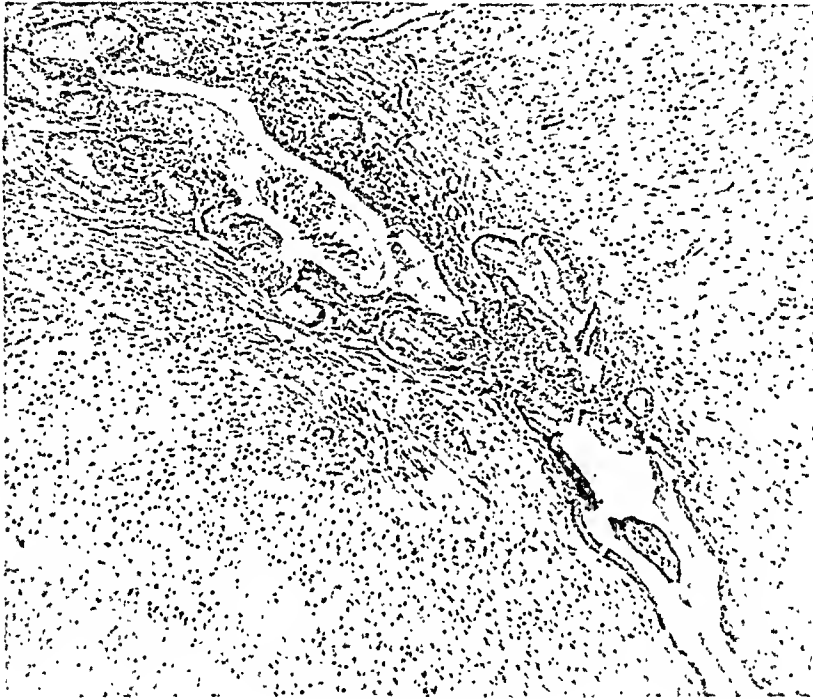


Fig. 1.—Case 1. The tumor can be seen surrounding and invading the tip of a cervical gland.

At operation the uterus was retroflexed and multiple petechiae were scattered over the anterior peritoneal reflection. No extension of the tumor was seen at operation and a wide excision of the cervix and vagina was performed.

The gross specimen consisted of a uterus with cervix and vaginal cuff. There was a small indented area on the anterior portion of the cervix. Section through this point showed a pink tissue extending into the usual pale fibrous tissue. Many small cysts 4 mm. in diameter were present in the cervical canal. The uterine cavity measured 6.5 cm. The endometrium measured 4 mm. in thickness and was pale and smooth except for a soft polyp measuring 18 by 9 by 3 mm. hanging from the fundus. The myometrium showed no abnormalities.

Microscopic sections through the cervix in the region of the puckered scar showed a peculiar type of diffuse edematous fibrillary hyalinization with partial squamous covering. This myxomatous tissue could be seen extending between the fibrous bundles of the cervix. These extensions of the tumor were composed of the myxomatous stroma with few cells. The portion of the tumor remaining in the cervix was quite deep, and in only one area was it near the surface. In some areas numerous fibrillary nerve bundles were seen.

The patient has remained in good health without evidence of recurrence, and is well one year after operation.

particles broke free easily. The uterus was enlarged by irregular nodulations on the anterior surface. Voided urine showed a trace of albumin. The hemoglobin was 11 Gm. per 100 cubic centimeters. The red blood count was 3,500,000, and the white blood count 10,400. The nonprotein nitrogen, blood chlorides, and blood sugar were within normal limits. The erythrocyte sedimentation rate was 25 mm. per hour.

A dilatation and curettage yielded large quantities of friable white, yellow, and red material which contained minute hard nodules. This was diagnosed as being an unusual malignant tumor, and total hysterectomy and bilateral salpingo-oophorectomy were performed. At operation a tumor of soft friable tissue of varied color was found extending into both broad ligaments and into the pelvic fascia beneath the bladder.

The specimen consisted of a uterus measuring 8 by 7 by 6 cm. The serosa over the fundus was smooth and glistening. However, in the region slightly posterior and inferior to the right broad ligament, there was a small soft yellowish papillomatous body measuring 18 by 13 by 6 millimeters. The lower portion of this was blood stained. Anterior to the right broad ligament, there was a finely granular area in the serosa. The whole uterus felt quite soft and boggy. Protruding from the cut end of the uterus was a soft, necrotic appearing, blood-stained mass. When opened, the uterine canal measured 6 cm. in length. The myometrium measured approximately 8 mm. in thickness. The remainder of the specimen consisted of soft, friable, variously colored tissue which ranged from a slate gray through yellow to red and brown. There was one large mass in the center which was polypoid and 6 cm. in diameter. It was this mass which presented from the uterine os. When this was reflected, the remainder of the tissue was made up of polypoid soft masses which varied in size from small, raised, rounded nodules a few millimeters in diameter to larger ones which measured 4 by 2 cm. in area and were raised 1.5 centimeters. Throughout these nodules, there were occasional firm round foci which measured a few millimeters in diameter. In other portions there were fairly extensive gelatinous areas between the large papillary bodies. In one place near the os there was a firmer area which felt and appeared to be composed of small cartilagenous nodules in a myxomatous stroma. On cut section the tumor masses were pale, soft, and variously colored. These ranged from red through yellow to white. On section through one portion a small quantity of clear fluid flowed forth from numerous oval-shaped cysts measuring 11 by 5 millimeters. Section through the yellowish body presenting at the cervix showed a pale orangish surface, and in the center it was soft and composed of alternate minute yellow and red areas. Each of the tubes measured 5 cm. in length. Through the base of one there was a rather firm area which was indistinctly outlined in the broad ligament. On the other tube there was beneath the serosa a small yellowish nodule measuring 8 mm. in its greatest diameter.

Microscopic examination of the uterine tumor showed a highly undifferentiated spindle and oval cell growth with wide areas of pseudocystic change and some areas of necrosis. The cells varied considerably in size. Some large hyperchromatic deformed nuclei and mitotic figures were also observed. Scattered throughout this tissue were small islands of anaplastic cartilage or cartilage-appearing material which showed a pink or bluish pink homogeneous matrix encmeshing anaplastic cells resembling chondroblasts. Several small islands of fairly well-developed cartilage were scattered through the tumor. The small islets of primitive cartilage and chondroblasts were near these adult cartilagenous centers. Other portions were composed of a myxomatous stroma which did not stain for mucin with either mucicarmine or thionin, but with phosphotungstic acid hematoxylin and Masson stain appeared as a fine network with many minute granules appearing throughout.

There were glandular areas present. These varied from simple cystic structures which were lined by low cuboidal epithelium to narrow glands in which the epithelium was columnar and even clumped in small papillations. Some of these resembled endometrial glands, but others lined by flat epithelium did not. This tumor was classified as a mesodermal mixed tumor, although the possibility of a highly anaplastic teratoma with sarcomatous elements was also considered.

CASE 2.—The second case was a 76-year-old white parous woman who was admitted to the hospital complaining of slight vaginal bleeding of twenty days duration. This was of sudden onset and was completely painless. In 1939 she was treated for nephritis and cardiac decompensation. After a prolonged hospital stay she was markedly improved and remained fairly active until her present illness.

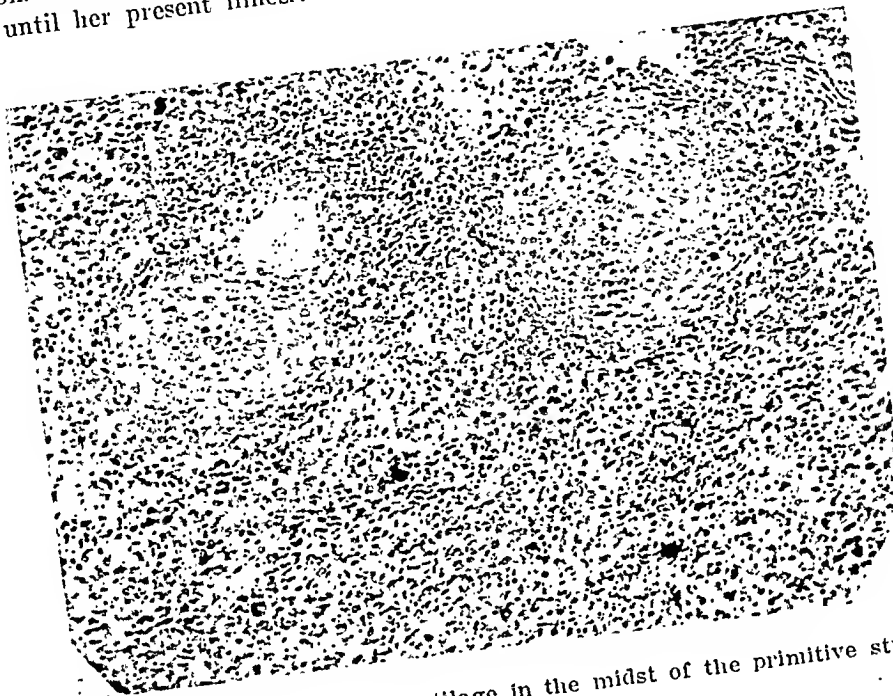


Fig. 4.—Case 2. A focus of cartilage in the midst of the primitive stroma.

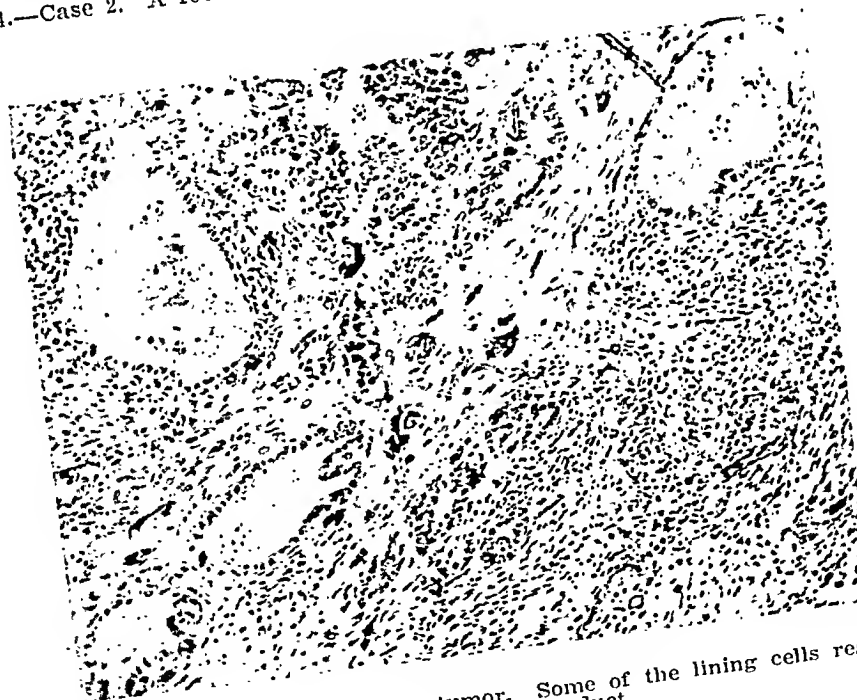


Fig. 5.—Case 2. Glands lying deep in the tumor. Some of the lining cells resemble the cells seen in the Wolffian duct.

Physical examination disclosed an accentuated second sound at the pulmonary and aortic areas, although the heart was not enlarged. Vaginal examination revealed a soft movable mass attached to the cervix. This was rounded, nodular and rubbery, and small

therapy have not been used extensively, despite the fact that the embryonal appearance of the tumor would lead one to believe that many of them would be radiosensitive. Total hysterectomy appears as the logical treatment if a wide excision of the surrounding tissues is accomplished. Meikel² suggested that this be followed by deep x-ray therapy, as a prophylactic against local recurrence or as a palliative measure. Shaw⁹ summarized the cases he reviewed by stating "The malignancy is extremely high and I can find no record of a patient recovering any length of time after removal of the growth. In most cases death rapidly follows operation."

Since our first case is apparently the smallest mixed tumor reported, we look forward to a more optimistic future than one would anticipate from a review of the reported cases. In this case, the tumor remained localized within the cervix of the uterus, and no evidence of extension could be found at operation. A case of multiple papillary hydropic tumors of the cervix and cervical stump occurring over a period of seven years with multiple operations, is described by Backer and Minich.¹⁶ When total hysterectomy was performed five months before death, a mixed tumor was found. The authors believed the tumors were parts of the same growth, despite the fact that the specimen from the first operation was not examined histologically. This appears to be the longest clinical course described.

Summary

1. Two cases of mesodermal mixed tumor of the uterus are reported: one a tumor of the fundus of the uterus with typical findings; the other a minute cervical neoplasm discovered incidentally by biopsy during a dilatation and curettage for uterine bleeding.

2. The cervical tumor was smaller than any other such tumor found in a review of the literature and therefore the prognosis appears good despite the gloomy outlook obtained from reports of other cases.

3. The discovery of an unusual and malignant tumor while still quite small again emphasizes the necessity for microscopic examination of all irregular areas of the cervix.

The authors wish to thank Dr. Ferdinand C. Helwig for his guidance and suggestions, and Dr. Lawrence P. Engel for permission to present the second case.

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Histogenesis

It is difficult to explain how a complicated tumor of embryologic structure should occur in different sites in the uterus. Basically, there are two schools of thought to explain this phenomenon: one by metaplasia or disturbance of development of the normal uterine components; the other by embryonal rests or latent anlagen which suddenly start growing under a stress of the organism.

Earlier writers were prone to accept metaplasia or degeneration of a specific uterine tissue as the origin of these tumors. Later writers tend to believe that in the complicated mixed tumors the question of metaplasia cannot be seriously considered because the many components and the embryonal character of the tissues indicates that the origin is due to individual primitive cell or mass tissue transplantation. Wilms was of the opinion that one particle of undifferentiated tissue had been transplanted, and from this anlage developed the most different formation. In mixed mesodermal tumors of the uterus this is thought to be a bit of the Wolffian duct, which must arise from caudad to kidney as no renal elements are found in these tumors, and migrates backward along the course of the ducts. The possibility that these tumors, found in the uterus and cervix, arise from the Wolffian duct is enhanced by Meyer's¹³ discovery of a Gartner duct in the uterine wall and the cervix of an adult. His later studies revealed a high incidence of Wolffian elements in the uterus. In a recent study Huffman¹⁴ found remnants of Wolffian ducts in approximately 1 per cent of cervixes studied by serial section.

Our attention was called to these tumors by Case 1 which aroused considerable interest both as to histologic diagnosis and as to prognosis. We have been unable to find any case in the literature where the diagnosis was made from an apparently routine biopsy without enlargement of the cervix or uterus. The biopsy was taken in an attempt to find the cause for uterine bleeding, although later examination revealed an endometrial polyp as the cause of the bleeding. It is interesting that almost 25 per cent of the cervical tumors reported by Meikel occurred at approximately 22 years of age, whereas the range is from 1 to 50 years of age. The minute size of this tumor leads to the belief that the growth may represent the earliest stages in the development of these tumors. The embryonic mesenchyme found in this tumor appeared to be the same as that described in the larger more complex tumors. This neoplasm had begun to develop a botryoid form, and in several areas it resembled microscopically the larger botryoid sarcomas of the cervix. Numerous authors have emphasized the difficulty in determining their malignant nature, and even at microscopic examination this may go undetected. One case (15) reported in 1939, had a recurring cervical polyp removed three times within ten months before its malignant nature was noted.

The second case is characteristic of uterine mixed tumors of the fundus both as to symptoms and as to pathology. Uterine bleeding, brownish foul discharge, and uterine pain or enlargement are the usual presenting complaints in tumors of the body of the uterus. These fundic tumors occur most frequently in the fifth decade of life; over 50 per cent of the reported cases were found in persons in this decade. The mixture of many tissues, all of which can arise from the mesoderm, including myxomatous tissues, cartilage and pseudocartilage and glandlike elements of a difficult nature to identify as to origin, is typical of these mesodermal tumors. The tubelike spaces in our tumor at first led to the diagnosis of a teratoma. Later these glands were taken to be inclusions of endometrial glands. However, the lining of some of the glands in this tumor was part flat cuboidal and did not resemble the lining of the endometrial glands, but did resemble the lining of the embryonic Wolffian duct. This patient began having a foul, blood-tinged discharge approximately ten weeks after operation. This increased gradually but the patient remained fairly active for five months after operation, at which time she became quite ill and died in another city two weeks later.

Prognosis

A review of the outcome of reported cases indicates that little has been accomplished in treating these tumors. All attempts at therapy have been futile. Radium and x-ray

In October, 1943, she again became pregnant. Progesterone therapy was considered advisable and was therefore instituted. The pregnancy progressed satisfactorily until the 7th month of gestation. At that time the patient complained of feeling faint; when she moved her bowels, the stool was copious and very fatty. Immediately afterwards, she vomited large amounts of coffee-ground material. Her symptoms were strongly suggestive of peptic ulcer. She was put to bed and transferred to the hospital where she was placed on an ulcer diet, and given vitamin K. She remained in bed six weeks prior to delivery, receiving several blood transfusions. She was delivered at term, July 23, 1944, of a normal, living, female child weighing 6 pounds 6½ ounces. She made an uninterrupted recovery from labor. Over a year later, she was apparently doing satisfactorily.

In October, 1944, she was x-rayed, and, although the ulcer could be visualized, she offered no complaints and at this date is feeling well.

CASE 2.—Patient C. B., white, aged 28 years. Menstrual history, onset at 12 years of age, every 28 days, for four or five days, no pain. This patient had the usual childhood diseases and no other illness of importance.

In January, 1939, the patient had a spontaneous abortion at 6 to 8 weeks.

In September, 1939, she had a spontaneous abortion at 4½ months. Following this abortion, the patient complained of symptoms suggesting ulcer. She was x-rayed, and peptic ulcer was diagnosed. She was placed on an ulcer diet and given medical treatment. Prompt response resulted in a twenty-pound weight gain. She came under observation again on July 9, 1940. At that time, examination revealed a six weeks' pregnancy. Physical examination was essentially negative. There were absolutely no ulcer complaints. Due to her previous obstetric history (two abortions), it was considered advisable to institute rest and progesterone therapy. Proluton was administered until the fourth month of pregnancy. At that time the patient had an attack of hematemesis, coupled with severe heartburn and a recurrence of ulcer symptoms. Vomiting persisted; the urine showed albumin and hyaline casts and acetone. During this period, the patient had several attacks of hematemesis. About one month later, she was delivered of a stillborn child; then followed a long convalescence. Throughout the entire pregnancy, both ulcer diet and treatment were maintained as before conception.

CASE 3.—Patient A. T., white, aged 26 years. Menstrual history, onset at 14 years of age, every 28 days for 5 days.

She was delivered of a male child Nov. 14, 1936, low forceps, moderate postpartum hemorrhage.

In October, 1939 she had a gastroenterostomy for peptic ulcer.

She last menstruated July 5, 1942. In September, 1942, following a threatened abortion, the patient was ordered rest and sedation. On Nov. 5, 1942, the abortion symptoms recurred, and progesterone was prescribed, resulting in a gradual improvement in the patient's condition.

Gastric Analysis, Dec. 7, 1942.—

Macroscopic: Large amount of mucus in residue.

Microscopic: Many pus and red blood cells and epithelial cells.

| Report: | Blood | Free Acid | Total Acid |
|---------|-------|-----------|------------|
| | + | — | 6 |
| | — | 28 | 41 |
| | — | 37 | 53 |

In March, 1943, she complained of nausea, vomiting, and melena. The same month she was delivered spontaneously of a premature living male child.

CASE 4.—Dr. Edward B. LeWinn's¹⁶ patient, white, aged 35 years. Menstrual history, onset at 13 years, every 28 days for four or five days, gravida ii.

This patient had a history of epigastric pain in 1930, and an appendectomy was performed in 1931. Her symptoms were not relieved. In 1938, she had a cholecystectomy, result-

PEPTIC ULCER IN PREGNANCY

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ABUNDANT evidence in medical literature shows peptic ulcer in the adult to be predominantly a disease of the male. Before puberty, the reported cases are distributed almost equally between the sexes.¹ After puberty, peptic ulcer occurs considerably more frequently in the male. Various authors have estimated the ratio of its distribution to be from 2 to as high as 4 males per female affected.^{2, 3, 4} The mortality statistics of the United States for 1937-1938 showed the sex ratio for duodenal ulcer to be 3.6 males per female.⁵

The reason for the lower incidence of peptic ulcer in women is not known, nor has a satisfactory explanation been advanced for the observation that it is in general a milder⁶ and also less fatal disease in women.⁷

Two distinctive features characterize peptic ulcer in the adult woman: (1) it is a relatively uncommon complication of pregnancy, and (2) all symptoms incident to it are ameliorated or abolished upon the advent of pregnancy. The rarity of peptic ulcer during pregnancy has been cited by several authors.^{8, 9, 10} Reviewing 70,310 consecutive pregnancy hospital admissions, Sandweiss et al.² found only one woman with active symptoms of ulcer. This finding is in sharp contrast to the common occurrence of other diseases of the gastrointestinal tract during pregnancy, such as appendicitis,¹¹ ulcerative colitis,¹² and cholecystitis.¹³ That pregnancy exerts a beneficial effect on ulcer symptoms is well known. Sandweiss et al.² reported 52 pregnancies in 25 women proved to have had peptic ulcer. During pregnancy, their ulcer symptoms disappeared in all but one case. To date, only 15^{14, 15} authentic cases of duodenal ulcer proved by autopsy have been reported during pregnancy. Although peptic ulcer complicating pregnancy is not a frequent occurrence, we have encountered several cases of it, but only after careful questioning and examination. Very often the ulcer symptoms are either masked or confused by the pregnancy, and therefore missed.

Pregnant women with no ulcer histories have been treated successfully with progesterone to prevent threatened abortion. Recourse to progesterone therapy might therefore be expected in cases of potential abortion during the pregnancy of women with histories of peptic ulcer. This treatment has actually been adopted on three occasions with distinctly drastic results.

These three cases together with a review of one in the literature¹⁶ appeared of sufficient interest to warrant reporting, since, to our knowledge, no mention has previously been made of the ulcer-aggravating effects of progesterone on pregnant women with histories of peptic ulcer prior to pregnancy.

Report of Cases

CASE 1.—Patient D. McK., white, aged 38 years. Menstrual history. Onset at 15 years of age, every 28 days for seven days, no pain. This patient had infantile paralysis at the age of 4 years and made a good recovery. In 1936 she suffered from "indigestion."

In 1937, this patient had an attack of hematemesis, and at times noticed tarry stools. Several attacks of hematemesis followed. The patient said she was hospitalized and placed on a milk and cream diet. She remained in hospital for three weeks; following this treatment, she returned home and was treated by her family physician for peptic ulcer and anemia. It took her six months to regain her normal status and return to work.

In May, 1942, she was delivered spontaneously, at 7½ months, of a macerated, stillborn male child; and, despite careful studies, no apparent cause could be found in either parent or child. During this gestation period the patient was free from ulcer symptoms.

admittedly not common, occurs perhaps more frequently than hitherto credited. In ulcer patients, its symptoms are said to abate during the first trimester of pregnancy. Consideration should be given to the possibility that, in some cases, peptic ulcer during the first trimester may be masked by, or misdiagnosed as, hyperemesis gravidarum. Indeed, this suggestion is supported by Mussey of the Mayo Clinic, who reports that of 370 necessary operations during pregnancy, over a period of ten years, two were for peptic ulcer.

To our knowledge, no reports have been published establishing progesterone as an ulcerogenic agent. In the normal nonpregnant and pregnant subject, it would appear not to react on the gastrointestinal tract. Only when an ulcer lesion is or has been present are the aggravating effects of progesterone evident. It would be interesting to determine whether administration of progesterone to a nonpregnant ulcer patient would engender the deleterious effects observed in the pregnant ulcer patient.

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ing in a temporary relief of her symptoms. She was then put on a course of nonsurgical biliary drainage. In April, 1945, she had a spontaneous abortion at six weeks. Her last menstrual period was July 27, 1945, her expected date of delivery May 2, 1946.

In view of this patient's history of previous abortion, she was maintained on progesterone throughout the present pregnancy. On March 18, 1946, the patient experienced epigastric discomfort about one to one and one-half hours after the ingestion of food. Her symptoms progressed, and she later noticed tarry stools and blood in the vomitus. On April 12, 1946, she suffered severe gastrointestinal hemorrhage; blood transfusions were repeatedly administered, and the patient was very ill. On April 17, 1946, there was a slight improvement in her condition, and on April 19, she was delivered of a stillborn, premature, macerated male child. On May 2, 1946, a fractional gastric analysis was made, and on May 3, x-ray examination showed evidence of peptic ulcer.

Discussion

A review of the literature reveals that duodenal ulcer occurs less frequently in women than in men and that it is a rare complication of pregnancy. In women known to have had peptic ulcer, its symptoms almost always disappear with the advent of pregnancy.

In the three cases reported of ulcer occurring during pregnancy, the history of each patient suggested or proved the existence of an ulcer prior to pregnancy. The ulcer symptoms abated during the early stages of the pregnancy in all three women; yet the later administration of progesterone was followed in each case by an aggravation of the ulcer, by hemorrhage, and a stormy course almost terminating fatally.

The relationship between sex and incidence of peptic ulcer has led several investigators to place peptic ulcer on an endocrine basis, and to attempt a sex hormone therapy. On the whole, the results of these investigations have been inconclusive. Among the sex hormones used for the treatment of peptic ulcer in the human being are included: estrogens,¹⁷ ovarian follicular hormones,¹⁸ estrones,¹⁹ and urinary chorionic gonadotropins.²⁰

Experiments conducted on dogs with surgically induced duodenal ulcers and on men with peptic ulcer have shown the administration of human pregnancy urine extracts to have a beneficial effect on the ulcer. Thus, in dogs with experimental Mann-Williamson ulcers, daily injections of extracts of pregnancy urine reduced the incidence of perforation from 72 per cent to 20 per cent and increased over-all benefits from 10 per cent to 85 per cent. While this would suggest that urinary gonadotropins have an antiulcer effect, the picture is unfortunately not at all clear. Recent work has shown the anti-ulcer factor to be present not only in the urine of pregnant women, but in the urine of non-pregnant women and men as well.²⁰

The relationship between progesterone and gonadotropin is such as to indicate possible antagonism between them. The reported beneficial effects of gonadotropin on peptic ulcer would suggest the adverse action of progesterone. Whether the respective actions of gonadotropin and progesterone affect the lesions directly or indirectly is not clear at the present time.

The history of peptic ulcer should place the obstetrician on guard when considering the application of progesterone against threatened abortion. We may further suggest that the incidence of peptic ulcer in pregnancy, while

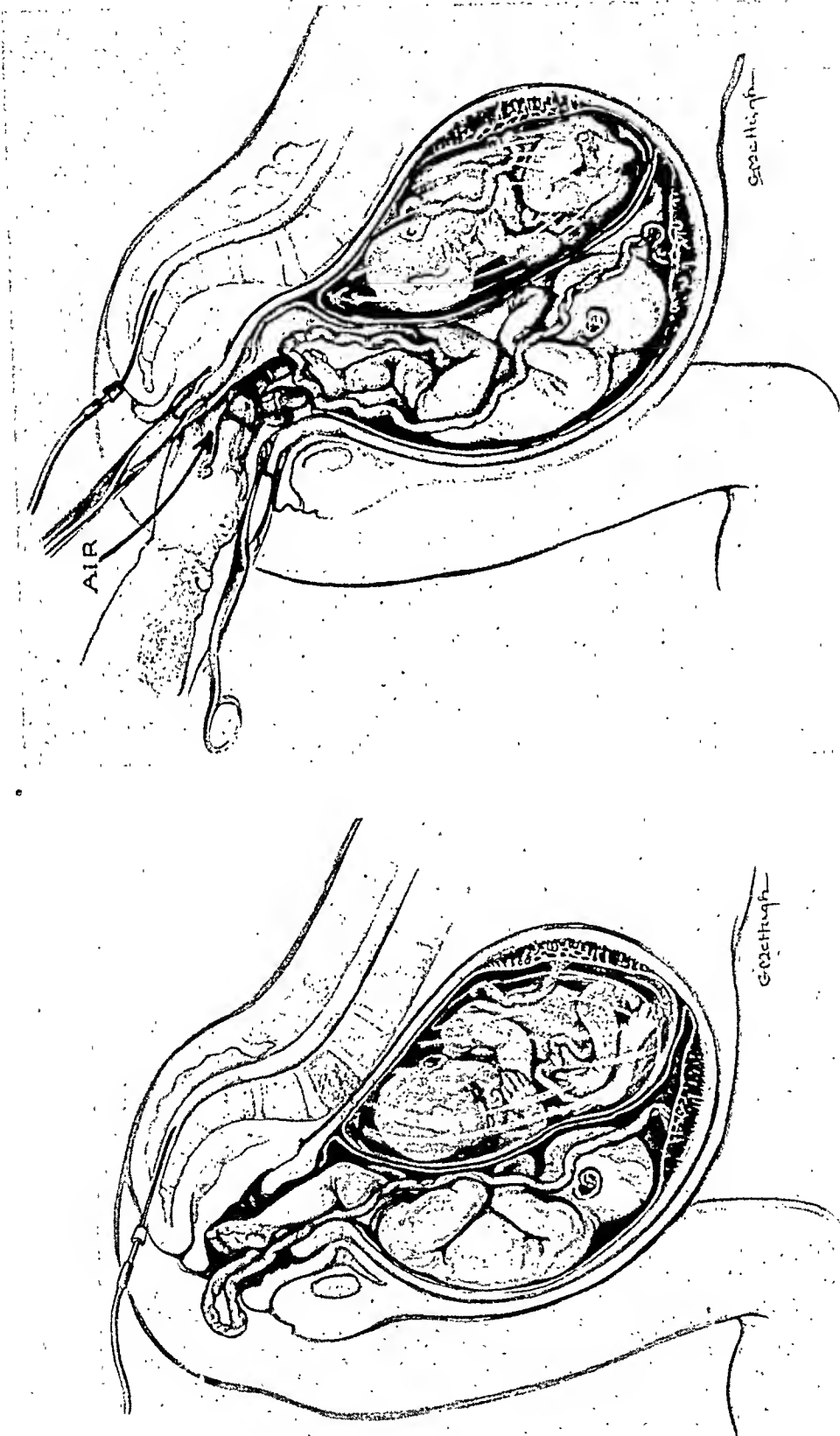


Fig. 1.

Fig. 2.

Fig. 1.—Shows patient in knee-chest position, needle in caudal canal, footling breech presentation of first twin with prolapse of cord and foot; cervix undilated and uneffaced.
Fig. 2.—Illustrates technique of replacement of prolapsed cord in knee-chest position. The cervix is grasped with sponge forceps and upward traction made by assistant; the operator's hand gently replaces cord and foot which are dropped down into uterus much as one would drop "a worm into a bottle." It is obvious that the amniotic sac becomes distended with air during this procedure.

VAGITUS UTERINUS IN TWIN PREGNANCY

With Prolapsus Funis and Its Treatment Under Continuous Caudal Analgesia

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VAGITUS uterinus, or the audible crying of the fetus in utero, is an unusual phenomenon of pregnancy first described in the literature by J. B. von Fischer in 1730¹ and renowned in legend and fable centuries before, Mahomet and St. Bartholomew having been said to have made themselves heard from the womb before birth.² Numerous such cases have been reported in the literature, and, in 1943, Ryder³ reviewed 123 authentic cases occurring between 1800 and 1941, including his own. Since 1941, a number of other cases have been cited, notably the observations of Thorp,⁴ Bourgeois and King,⁵ Mitchell,⁶ Kitzmiller and Mitchell,⁷ Rucker,⁸ and M. A. Lewis.⁹ Kitzmiller and Mitchell,⁷ as well as DeLee,² emphasize the necessity of fulfillment of the following conditions before intrauterine crying is possible: (1) The membranes must have ruptured. (2) There must be some manipulation to stimulate the fetus. (3) Air must enter the uterus, or this last requirement may be satisfied by the production of gases within the uterine cavity. It is noteworthy that the cases reported by Thorp, Rucker, and Lewis, like the one herein presented, were conducted under caudal analgesia, while that of Mitchell also involved prolapse of the umbilical cord.

Case Report

This patient was a 34-year-old white woman who had previously had three normal deliveries. At the seventh month, a diagnosis of twin pregnancy was confirmed by x-ray. On the morning of Aug. 14, 1947, at full term, the membranes ruptured at home, and, shortly thereafter, her physician-husband noted that the umbilical cord was protruding from the vagina. She was immediately hospitalized, where it was observed that the prolapsed cord was still pulsating normally. The patient was not in labor and there were no uterine contractions. Continuous caudal analgesia was induced at once, using 1.5 per cent Metycaine administered by the technique of Hingson and Edwards.¹⁰ As soon as analgesia was complete and the blood pressure stabilized, the patient was placed in the knee-chest position (Fig. 1) and the vulva and perineum surgically prepared and draped. Inspection now revealed that a foot, as well as the cord, was lying in the vagina. The cervix was thick and admitted only three fingers. It was grasped with sponge forceps (Fig. 2) and drawn upward as the gloved hand pushed the foot downward into the fundus and replaced the cord much as one might drop a worm into a bottle. It is obvious that during this manipulation the amniotic sac must inevitably have been ballooned up with air by atmospheric pressure (Fig. 2), and thus all of the conditions outlined by DeLee and by Kitzmiller and Mitchell were fulfilled. A large-sized Voorhees bag was now inserted into the uterus and tightly distended with water (Fig. 3), and the patient allowed to resume the dorsal position, the bag preventing escape of the trapped intrauterine air. The air-distended amniotic sac, completely drained of fluid, provided an ideal medium for respiratory movements and for the transmission of sound, oxygen supply to the fetus being still continuously supplied by way of the pulsating umbilical cord.

About one hour after the insertion of the bag, regular uterine contractions began and, after another hour, the patient and observers were amazed to hear the cry of the unborn fetus. This cry was no weak sound, audible only with the stethoscope, but was identical in every way with the wail of a newborn babe and was plainly heard by nurses and doctors all over the room. Crying continued for one and one-half hours until delivery and would follow each uterine contraction. The cervix was now completely dilated and the bag was expelled from the vagina. The first twin, a 5 pound, 11 ounce girl, was delivered by breech extraction, could be

4. The widespread notoriety given this case in the public press has brought to light a number of similar experiences, hitherto unreported, making it quite obvious that the condition is more common than we have supposed.

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136 WEST McMILLAN STREET.

heard crying during the manipulations incident to delivery, and made definite efforts to escape the grasp of the operator during the procedure. The infant was well developed and cried lustily immediately after birth, being none the worse for the experience.¹¹ The second twin, a 4 pound, 11 ounce girl, was delivered promptly by version and extraction after artificial rupture of the membranes.

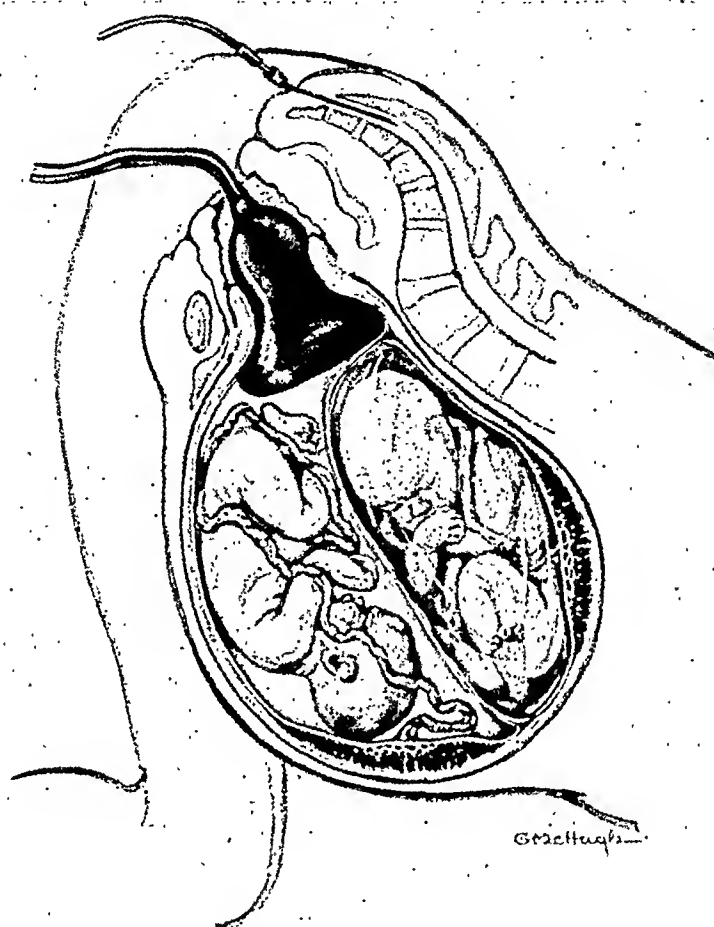


Fig. 3.—Shows large Voorhees bag inserted into uterus and distended with water, preventing recurrence of prolapsus funis, and incidentally "trapping" air in the uterus and continuing the balloonlike distention of the amniotic sac of the first twin.

This case of vagitus uterinus serves to emphasize a number of important facts:

1. Continuous caudal analgesia, as in the cases reported by Thorp, Lewis, and Rucker, apparently made intrauterine crying more likely because the baby was not depressed by sedatives or narcotics; Rucker believes that the condition is destined to become more common with the more widespread use of regional nerve block anesthetics.

2. An often neglected method of replacement of the prolapsed cord is presented, and is obviously made more practical and effective under the conditions of patient cooperation made possible by continuous caudal analgesia, one of us (J. G. C.) having used the method successfully on two previous occasions without any anesthetic agent whatsoever.

3. While vagitus uterinus has classically been considered to be a sign of intrauterine asphyxia, and while in Ryder's collected series of cases the fetal mortality approaches 20 per cent, the conclusions of Peters¹² that "fetal mortality following vagitus uterinus is in practically all cases attributable to mechanical injury suffered by the fetus during the course of ill-advised procedures to effect hasty delivery." seem to be justified. As in every other obstetric emergency, the operative procedure elected should be carefully, intelligently, and deliberately selected. Haste is never indicated!

I. M. V., 55-year-old white woman, single, no reported pregnancies. Referred to the Roswell Park Memorial Institute Aug. 6, 1947.

Past History.—Usual childhood diseases and rheumatic fever. Menstrual history: Menses began at 13 or 14 years, occurred every 28 days, lasting 4 to 5 days. December, 1944: Mikulicz operation for lesion of the sigmoid; left salpingo-oophorectomy.

Present Illness.—Patient has had metrorrhagia and menorrhagia periodically since 1942. She had a severe hemorrhage in June, 1947, and a dilatation and curettage were done July 5, 1947. Pathologic report was adenocarcinoma of the uterus. Patient referred to this institution.

Physical Examination.—General examination was essentially negative. Well-healed lower abdominal scar, no masses palpable. Weight 128 pounds.

Pelvic examination: cervix appeared negative and blood was coming from the external os. Fundus not palpable. Canal measures 3 inches and heavy curettings were obtained with the Novak curette. Possible broad ligament extension on the left but it might be postoperative scarring.

Laboratory Examination.—Hemoglobin 70 per cent. Red blood count 3.5 million. White blood count 7,000. Normal differential. Urine, negative. Blood sugar: 106. Non-protein nitrogen, 29. Albumin 3.23. Globulin 2.69. Chlorides 472. Cholesterol 161. X-ray of chest, pelvis, and lumbar spine, negative. Electrocardiogram, sinus tachycardia.

Treatment.—August 6, radium tubes 3 by 15 mg. for 133 hours—6000 mg. hr. Readmitted to hospital Sept. 26, 1947. September 30, panhysterectomy performed. Patient discharged in good general condition on Oct. 13, 1947.

It is interesting that in both cases the uterus showed multiple leiomyomas and the adenocarcinoma was anaplastic and showed evidence of muscular invasion. Furthermore, although there was an interval of over four years between admissions of the two patients, their symptoms of irregular bleeding date back to approximately the same time in each case. It cannot be proved, but it is possible, that either a malignant or premalignant condition existed in the second patient at the time of the illness of her sister four years ago.

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ADENOCARCINOMA OF THE UTERINE FUNDUS IN IDENTICAL TWINS

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(From the Roswell Park Memorial Institute)

CASES of tumors in twins have always been of interest to geneticists and physicians. In reviewing the literature for the past twenty years we were unable to find a case of uterine fundus carcinoma in monozygous twins. Cerebellar tumors,¹ lymphocytic,² and chronic lymphatic leukemia,³ retinoblastoma,⁴ carcinoma of the stomach,⁵ carcinoma of the breast,^{6, 7} and adenocarcinoma of the large intestines,^{8, 9} have been reported in twins. Dr. Madge T. Macklin, Research Associate in the Department of Medicine at Ohio State University, who has done a great deal of work in tumors in twins, states that she does "not know of any other case in which carcinoma of the fundus in each member of an identical twin pair has been reported."¹⁰

In assuming that these twins were identical, we did not rely on the statements of the patients and family, but made every effort to disprove their identity. The patients were identical in skin coloring, height, weight, and the color of their eyes and hair. Also, they frequently took each other's examinations while in school and only the most intimate members of the family could tell them apart.

In attempting to disprove their identity, Dr. Ernest Witebsky of the University of Buffalo examined their blood and each patient was: Blood Group: A, subgroup A₁; Rh positive, Subtype Rh₁Rh₂; and blood type M.¹¹

Furthermore, Professor of Genetics D. C. Rife of Ohio State University examined the fingerprints of these patients and reported that "in this pair there are more than the average degree of differences between right and left hands, and the fact that these differences are as great as those between the two rights and two lefts of the pair suggests that they are probably identical."¹²

Case Report

The family history of these twins was irrelevant, except for the fact that the mother died of carcinoma of the ovary at the age of 52.

I. F. V., 50-year-old white woman, single, no reported pregnancies. Referred to the Roswell Park Memorial Institute on Jan. 11, 1943. The history included the usual childhood diseases, typhoid fever, influenza, and rheumatic fever. Menstrual history: Menses began at 14 years, occurred every 28 days, lasting 4 to 5 days; occasional back pain with menstrual flow.

Present Illness.—The patient first noted pain in the abdomen in November, 1941. In January, 1942, she had intermenstrual bleeding with clotting during the menses periodically until August, 1942, at which time she had profuse continuous bleeding. On Nov. 13, 1942, she had a subtotal hysterectomy for a fibroid uterus. The pathologic report was multiple subserous fibromyomas, submucous fibromyoma, and adenocarcinoma of the corpus uteri. The patient was referred to this institution.

Physical Examination.—Thin, nervous, anemic-appearing white woman weighing 115 pounds. General examination essentially negative.

Pelvic examination: no discharge; cervix deformed, feeling slightly nodular on the left posterior; stump of the cervix movable. Blood count: hemoglobin 47%, red blood cell count 3.5 million. Urine: negative.

Treatment.—Jan. 11. 6 1-mg. seeds implanted in cervix. Dosage 798 mg. hr.

Jan. 11 to Feb. 2. 200 kv. x-ray to anterior and posterior pelvis for total skin dosage of 3,300 r.

April, 1943. Asymptomatic with no evidence of disease.

August, 1947. Report from a mental institution: hypertension and senile vaginitis with no evidence of recurrent disease.

Blood Chemistry.—

| | | |
|---------------------|----------|--------------|
| Sugar | 100 | mg./100 c.c. |
| Nonprotein nitrogen | 57 | mg. per cent |
| Serum albumin | 4.29 | |
| Serum globulin | 2.00 | |
| Total blood protein | 6.9 | mg. per cent |
| Wassermann | negative | |
| Transfusion type | 0 | |

Chest X-ray.—Revealed a marked elevation of right diaphragm and right pleural effusion. The heart shadow was shifted markedly to the left and the right lung was completely collapsed.

Thoracentesis Fluid.—In eight days of observation, in 3 taps, over 12 L. of fluid were removed. This had a low cell count, chiefly plasma cells, specific gravity of 1.040, and no bacteria grew on guinea pig inoculation or upon prepared media.

On July 30, 1947, with a tentative diagnosis of Meigs' syndrome, and under lumbar spinal anesthesia, the abdomen was opened, to reveal about 2,000 c.c. of straw-colored fluid and a large tumor of the left ovary, firmly embedded in the lower abdomen. Following freeing from a tenaceous exudate, the tumor was removed and the abdomen closed in layers with quilting cotton, without drainage. During the operation, a transfusion of 500 c.c. of whole blood was given, followed by 1,000 c.c. of 5 per cent glucose in normal saline intravenously.

Pathology.—Grossly the specimen consisted of an encapsulated, exudate-covered, mass measuring 24 by 20 by 8 cm., weighing 2,800 Gm. The tumor was firm and cut surface showed interlacing bundles of fibers in a grayish stroma.

Microscopic.—Sections showed stellate cells with spindle-shaped nuclei, arranged in bundles having an interlacing pattern. No disturbance of uniformity or growth activity was noted.

Diagnosis.—Fibroma of the ovary.

Postoperatively, the patient was ambulated as usual sitting at the bedside in twenty-four hours and walking twice daily each day thereafter. The convalescence was uneventful except for a bout of paroxysmal tachycardia on the third postoperative day. Following the reduction to a normal rhythm by rapid digitalization, the patient followed the usual pattern and was sent home on the seventh postoperative day.

A follow-up after two weeks revealed that no fluid could be shown to be present in either chest or abdominal cavity. The patient was feeling quite well and had resumed her normal duties around her home.

It is again emphasized by this, the forty-sixth case reported, that any patient who exhibits the characteristics described and who presents the triad of pelvic tumor, ascites, and hydrothorax should have the benefit of operative exploration, no matter how hopeless the condition may appear.

310 CHAMBERS STREET,
GLEBORNE, TEXAS.

MEIGS' SYNDROME

W. R. WHITEHOUSE, M.D., AND R. W. KIMBRO, M.D., CLEBORNE, TEXAS

IN 1937 Meigs and Cass presented histories of four patients who had ascites and hydrothorax associated with fibroma of the ovary. The phenomenon was immediately relieved in each case by the successful removal of the ovarian tumor, and such has been the story with most of the total of 45 cases reported. Each case has demonstrated the important fact that, although the patient presents a picture of hopelessly far-advanced malignancy, a phenomenal cure may be obtained. Apparently, the major limitation is with the knowledge of the doctor who first observes the case.

As in the case seen by us, physicians not including this syndrome in their differential diagnosis are likely to avoid the risk of a possible postoperative mortality, and thus condemn the patient to a slow death resultant from repeated thoracentesis and paracentesis. Successful recovery of each case stands as a monument to the keen observance of the authors of the original communication.

A number of questions remain unanswered, such as the mechanism of production of the probably identical fluid in the pleural and peritoneal cavities. The most likely explanation of the pleural fluid is that the "one way" pathways from abdomen to chest are lymphatics; first by way of the interstices of the cells under the diaphragm, thence to the subdiaphragmatic lymphatics, and thence into the chest.

Case Report

L. H., aged 48 years, white, para iii, gravida iii, married, was first seen July 12, 1947. The patient complained of extreme dyspnea which had been progressive for one week, having begun at the time she had "intestinal influenza" with diarrhea and fever. She had consulted a doctor who had made a diagnosis of advanced malignancy and had recommended paracentesis. For the two previous years she had noticed a swollen abdomen and a hard mass located in the lower region, which caused no more symptoms than those due to its bulk. The family history, as well as social, medical, and surgical was negative. The menses were scant but regular and she had conducted a normal housewife's existence prior to the relatively acute onset of dyspnea.

Physical examination revealed a cachectic, white, sthenic, woman appearing older than her stated age, and laboring for breath. Her weight was approximately 135 pounds; blood pressure 130/85; temperature 102° F., pulse 120 per minute, and respirations 60 per minute, even with oxygen furnished by pharyngeal catheter.

Examination of the chest showed complete flatness to percussion and an absence of breath sounds on the right. By percussion, palpation, and auscultation, the heart was shifted markedly to the left but was irregular only in the rapid rate. The abdomen was protuberant and symmetrically enlarged to the size of a seven months' pregnancy. Shifting dullness in the dependent portion was elicited, as well as a fluid wave. No viscera were palpable; however, a large firm, movable mass, about the size of a seven months' pregnancy filled the lower abdomen.

Clinical evaluation revealed the following:

Blood Count.—Hemoglobin 13.2 Gm., red blood cells 3.8 million, white blood cells 14,150, differential normal.

Blood Sedimentation Rate.—42 mm. (normal 12 mm.).

Urine.—Specific gravity 1.022, albumin 1 plus, sugar negative, microscopic, occasional pus cell.

Reduction in the size of the uterus, in the quickest manner possible, in order to allow the surgeons ample time for exploration and repair, was the paramount reason for the decision made. Considering the possibilities of postoperative infection, it was realized that cesarean hysterectomy would give the patient a better prognosis. However, the necessity for rapid surgery overruled this argument. Under favorable circumstances, a cesarean hysterectomy is a more prolonged operation than a classical section.

The threat of infection was overcome by the administration of both the sulfonamides and penicillin.

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BULLET WOUND OF A GRAVID UTERUS WITH INTESTINAL PERFORATION

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(From the Fitkin Memorial Hospital)

IT WAS considered advisable to report this case, not only for its interesting potentialities, but also for the paucity of information in the literature.

Mrs. E. J., 31 years of age, 8 months pregnant, gravida iii, para ii, was admitted to the surgical service of the Fitkin Memorial Hospital, at 3 P.M., on Aug. 16, 1947. Shortly before admission, she had sustained three bullet injuries to the body. A bullet wound of entrance was found in the upper right quadrant of the abdomen, with point of exit in the mid left flank, the bullet unquestionably having perforated the uterus. There were two wounds of the lumbar dorsal area of the back which, although bleeding profusely, were considered to be flesh wounds. The left index finger had been fractured by a third bullet injury.

The innoeous external appearance of the injuries belied the serious nature of her general condition. The patient was pale and covered with a cold perspiration; the pulse was rapid, feeble but regular; the blood pressure was 118/64. There was evident apprehension and moderate air hunger. She complained of severe and steady abdominal pain. All the symptoms pointed to internal bleeding with impending shock. The uterus was hard, tense, and exquisitely tender to palpation. The fetal heart was indistinctly heard in the beginning but soon was lost.

The patient was given intensive shock-control therapy, including blood plasma and whole blood intravenously. Under spinal anesthesia, the abdomen was opened through a left paramedian incision, its midpoint being the level of the umbilicus. Upon opening the peritoneum about 300 c.c. of free blood were found in the peritoneal cavity. Examination of the uterus revealed two ragged perforations on the anterior and posterior fundal surfaces, each about 1 cm. in diameter, which were bleeding freely. A classical cesarean section was performed and a stillborn infant delivered. The infant had not been injured by the projectile. The placenta was found free in the fundal area. It had been perforated and separated from its bed by a large retroplacental hematoma. The uterine incision was closed in two layers; the first layer interrupted and the second a continuous Lembert. Both perforations of the uterus were closed with mattress sutures, controlling the bleeding. With the uterus emptied of its contents, it was then possible to explore the abdomen for further injuries. Investigation of the abdominal organs revealed multiple perforations of one segment of the midportion of the ileum. Accordingly, about two feet of intestine were resected and continuity restored by an end-to-end anastomosis. There being no further evidence of injury, the abdomen was closed in layers without drainage.

The postoperative course was without morbidity. The only cause for concern was abdominal distention which was controlled by siphonage. The usual medication for the control of infection was resorted to, including blood transfusions, sulfonamides, and penicillin. The patient was discharged on Aug. 31, 1947, in good condition.

Comment.—The only controversial question in this case involves the choice of procedure in handling the injuries to the gravid uterus at operation. This problem was thoroughly discussed prior to operation. Would a cesarean hysterectomy rather than a classical section be the choice procedure? The weight of the evidence favored the classical section.

mesentery, and had numerous "tracks" on its surface, as if scraped with a curette. This gangrenous bowel dipped through a hole into the uterus. The uterus was enlarged and ante-posed. The perforation was about 3 cm. in length and in the midline just above the level of the internal os.

The bowel was ileum and both the proximal and distal ends of normal attached bowel were located. The denuded and gangrenous bowel was removed, bleeding areas in the mesentery were ligated, the mesentery was approximated, and the bowel united by an end-to-end anastomosis. Although plasma and blood were given during the operation, the patient's pulse rate began to rise. It was then deemed best merely to evacuate the uterine contents, rather than do a hysterectomy. The perforated area was extended by incision into the fundus along the posterior wall of the uterus. The uterus contained placental tissue and denuded bowel. An assistant grasped the hemostat that had been left attached to the bowel in the vagina and removed that which had been in the uterus through the vagina. The placenta was peeled off manually. The uterus was sutured with three layers of continuous catgut. The abdominal wall was closed in the usual manner and without drainage.

The immediate postoperative condition was good. The patient was placed on a regime of intravenous nourishment with 500 c.c. of whole blood, 1,000 c.c. Amigen, and 1,000 c.c. 5 per cent glucose in saline daily. No oral food or liquid was allowed. 500 mg. streptomycin and 100,000 units penicillin were given intramuscularly every three hours.

The postoperative course was surprisingly smooth. Her highest temperature was 101.4° F., and she was afebrile after the fifth day. The pulse remained below 100 at all times. Bowel activity was good, with the passage of flatus and a soft stool within forty-eight hours.

On the third postoperative day, symptoms of a generalized peritonitis and ileus developed. The abdomen became markedly distended and profuse vomiting occurred. Peristaltic sounds were diminished, yet the patient was mentally bright and not at all toxic, temperature 101° F. and a pulse of 80. This rapidly responded to decompression therapy, (namely Wangensteen suction, rectal tube, and small enemas) within twenty-four hours. Numerous liquid defecations followed.

By the sixth postoperative day, the patient was taking food and liquids orally. Antibiotics and intravenous medication were stopped at this time. She was allowed to be out of bed on the eighth day, and went home on the twelfth postoperative day.

Follow-up examinations show her to be in excellent health. In January, 1948, she questioned her status regarding future pregnancies. Her menses were normal. Examination revealed normal pelvic structures. Gas insufflation showed nonpatency of the Fallopian tubes. This latter test was repeated at biweekly intervals through March with the same result. In April, 1948, this test showed patency of the tubes at 140 mm. Hg pressure. An x-ray with radiopaque material visualized normal pelvic organs and patent Fallopian tubes.

This case is reported, not only because of the dramatic and unusual factors involved, but because it demonstrates the following points:

1. Patients who have had a recent criminal abortion should be examined for evidences of possible uterine perforation and bowel injury.
2. Uterine perforation in itself may not lead to shock or internal hemorrhage.
3. When operation is indicated, suture of the perforated uterus may be preferred to hysterectomy.
4. The value of blood, intravenous protein therapy, and the antibiotics is well shown by the final result in this case.

30 N. MICHIGAN AVE.

PERFORATION OF THE UTERUS FOLLOWING A CRIMINAL ABORTION WITH PROTRUSION OF GANGRENOUS BOWEL INTO THE VAGINA*

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(From the Henrotin Hospital, Chicago)

At 11:00 P.M. on Sept. 26, 1947, a woman, her husband, and her alleged abortionist came into the emergency room of the Henrotin Hospital, under the following circumstances:

The patient had believed herself to be about three months pregnant. Her husband was elated, but she wanted an abortion. When the husband came home on the night mentioned, he found a message from his wife saying she had gone to a physician's office to have an abortion. The husband phoned the doctor at once, and told him not to do anything until he got there, that he was on the way. The husband rushed to the doctor's office. When he got there, the reception room was empty, but he noticed a light in the treatment room. He broke into this room. He found his wife lying asleep on the examining table. The doctor, with instruments in his hand, was sitting at the foot of the table and the floor was covered with blood. The husband threatened violence and forced the doctor to drive all three of them to the Henrotin Hospital. As soon as they arrived, the husband telephoned his personal physician, Dr. William Jack, who referred the problem to the author.

The patient was a 30-year-old white primigravida. She was sleeping lightly, but was easily aroused and well oriented. She admitted going to a doctor for an abortion. She recalled lying down on an examining table. She remembered the doctor giving her an injection in the vein of her left arm and telling her to count to twenty. The next thing she recollected was sitting in a car next to her husband.

She complained of nausea and lower abdominal pain. Her blood pressure was 110/72, temperature 98° F., pulse 88, respirations 22. Her skin was warm and moist. She seemed drowsy but not acutely ill. The cubital area of the left arm had a small recent puncture wound. The abdomen was not distended, but was soft and markedly tender below the umbilicus. An iodoform gauze pack was protruding from the vulva. This small vaginal pack (12 inches long) was removed and a sterile speculum inserted. Old blood and small clots were noted on the vaginal wall. The cervix had a recent bilateral laceration. A large amount of grayish blue tissue protruded from the cervix into the vagina.

The impression was that of an incomplete abortion. Due to the history of the interrupted operation, it was decided to transfer the patient to the operating room for examination under light anesthesia and removal of the tissue in the cervical canal.

Due to prolonged questioning by the police and states attorney's office, the operative procedure was delayed. The anesthetic was started at 2:25 A.M.—about four and one-half hours after the incident in the doctor's office. The patient's condition at this time was good, blood pressure 118/80, pulse 84, respirations 20, skin warm and moist. Pelvic examination at this time disclosed a uterus about the size of an eight to ten weeks' pregnancy. The small bilateral cervical lacerations were again noted. The tissue protruding from the external os was blue-gray in color, flat, and had the appearance of fetal membranes that had been torn and scraped. This tissue was grasped with a hemostat. Upon making gentle traction, large amounts of this tissue—about 24 inches long—fell into the vagina. It had a dark blue color and proved to be gangrenous small bowel, previously torn from the mesentery, with marks of previous trauma from grasping and scraping. A hemostat was placed on this tissue close to the cervix and the remainder amputated.

A laparotomy was performed at once through a median infraumbilical incision. A small amount of free blood and dark clots (about 150 to 200 c.c.) were in the lower abdomen. A large area of small bowel (estimated at six feet) was gangrenous, denuded from the

*Presented before the Chicago Gynecological Society, Nov. 21, 1947.

instances of multiple pregnancy in her family. The personal history and the physical and laboratory findings were negative. The prenatal course was uneventful except for an episode of vaginal hemorrhage Nov. 7, 1946. This bleeding subsided with only conservative management, and the patient went on to term, when she delivered spontaneously a living female infant on May 8, 1947, after labor of only eight hours and 40 minutes.

The placenta of this infant weighed 456 Gm. and it measured 21 by 12 by 3 cm. On the maternal surface there were three separate ischemic and partially fibrotic cotyledons. On the fetal surface there was a fetus papyraceous of 50 mm. crown to heel and 34 mm. crown to rump in length (Fig. 1). This fetus was attached by an umbilical cord 25 mm. in length to a slightly thickened fibrotic area three cm. removed from the margin of the normal placenta. The atrophied placental site adjacent to but separate from the larger placenta establishes this as a binovular twin pregnancy (Fig. 2).

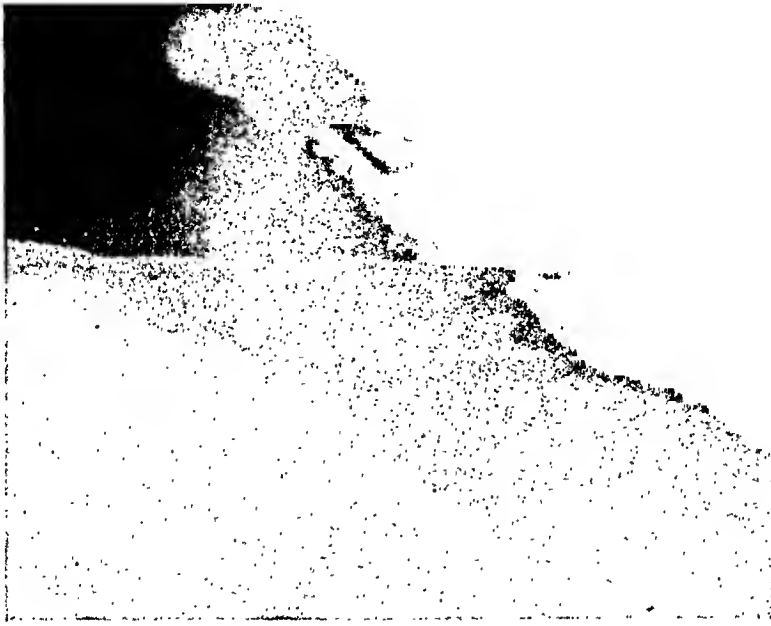


Fig. 2.—X-ray demonstrating the fetus papyraceous and its placental site.

Measurements of the fetus papyraceous, differentiation of the limbs, development of the face, and the erect position of the head suggest the age of this fetus to be approximately 10 weeks. The time of the arrest of this blighted fetus may be directly correlated with the time of the incident of the prenatal hemorrhage.

Summary

A case of fetus papyraceous is presented, in which the time of the fetal death may be chronologically correlated to an incident of prenatal vaginal hemorrhage.

The possibility of the disclosure of the intrauterine death of one or more fetuses of a multiple pregnancy as a result of such an episode indicates the need for careful interrogation for a history of ancestral multiple pregnancies; for alert evaluation of the first half of the period of gestation; and for the close scrutiny of the secundines.

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FETUS PAPYRACEOUS IN BINOVULAR TWIN PREGNANCY*

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THE disclosure of a blighted partner, or of blighted partners, at the delivery of a viable fetus is rare and interesting. A scrutinizing review of the literature by Kindred¹ (1944) revealed only 180 such cases.

In 1937, Collins² stated that fetus papyraceous occurred particularly in twin pregnancies. Siegler,³ in the same year, suggested that prenatal episodes of vaginal bleeding or of the development of toxemia were significant as warnings of the intrauterine death of one or more feti in multiple pregnancies. Ter Kuile and Parmalee⁴ (1944) stressed the practical value of close attention to the history as well as to the physical findings of patients during the period of gestation.

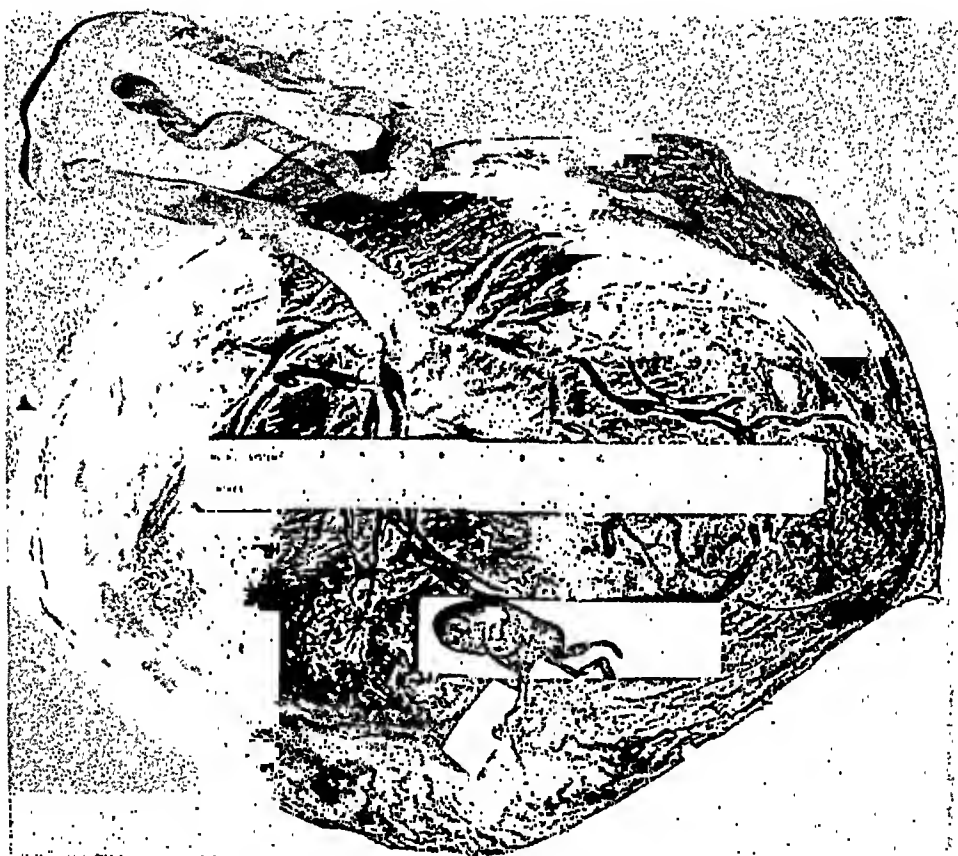


Fig. 1.—Fetus papyraceous attached to the fetal surface of the normal placenta.

Because of the relative infrequency of reports of fetus papyraceous in the literature, we present a report of a typical case in which a prenatal episode of vaginal hemorrhage prophesied the death of one of the fetuses of a binovular twin pregnancy.

Mrs. L. J., a 29-year-old, white female, gravida i, was first seen Oct. 22, 1946. The expected date of confinement was May 22, 1947. She related that there were numerous

*Presented at a meeting of the Chicago Gynecological Society, May 16, 1947.

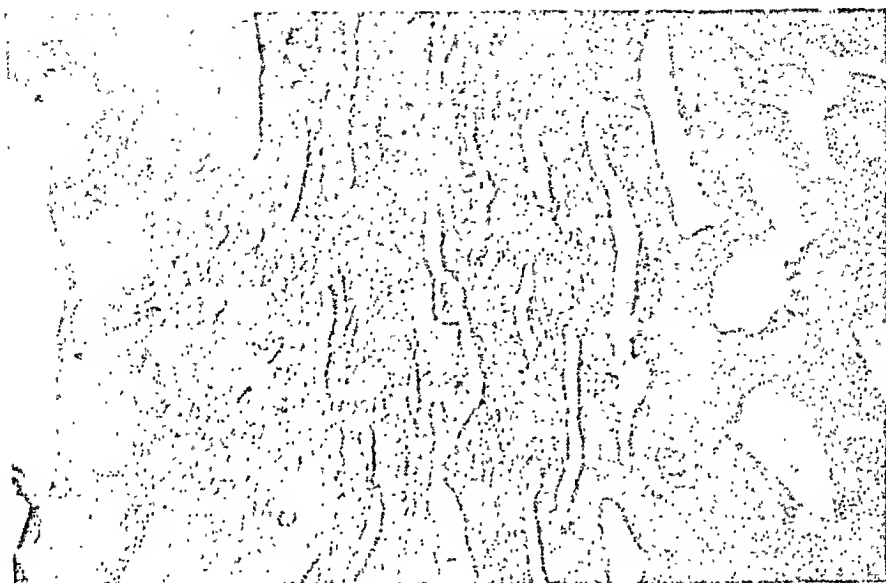


Fig. 1.—Photomicrograph (X80) showing the portio vaginalis, with numerous dilated venous spaces occupying the superficial portion of the cervix.

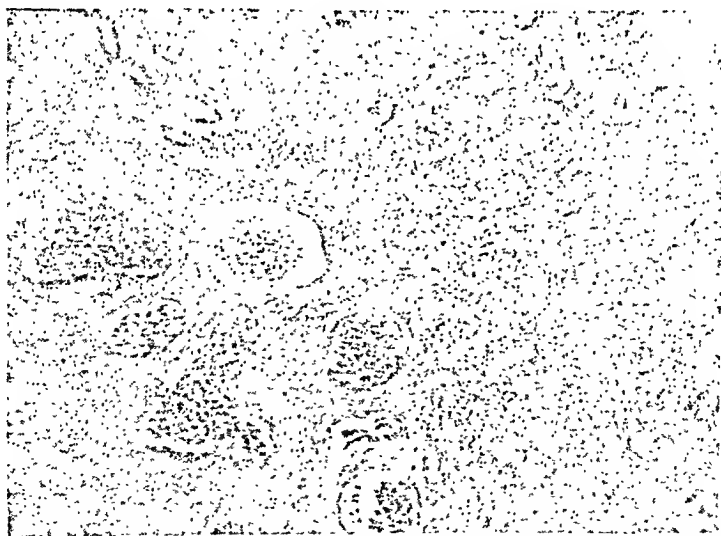


Fig. 2.—Deeper cervical tissue in the region of the cervical glands showing dilated venous spaces filled with erythrocytes.

HEMANGIOMA OF THE CERVIX

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AMONG the pathologic lesions occurring in the human cervix there is a wide variety of benign and malignant processes. However, the standard textbooks fail to mention the existence of angiomatous lesions of the cervix. Both lymphangiomas and hemangiomas of the uterine fundus have been described, and hemangioma of the broad ligament has been noted. The only articles on hemangioma of the cervix found in a review of the world medical literature for the last ten years are those by Machado and Junqueira,^{1,2} who reported six cases. So far as we have been able to determine, no case of hemangioma of the cervix has been reported in the English literature. Such a case recently came under our observation.

Report of Case

Mrs. R. F. P., white, aged 39 years, complained of numerous ailments, chiefly lower abdominal discomfort prior to the menses. This pain was suprapubic in location and varied in intensity. Occasionally, when severe, nausea and vomiting were also present. Backache was constant and bearing down pain was experienced with activity. Urinary stress incontinence was moderate. Dyspareunia, similar to the lower abdominal pain, was frequently noticed.

The menstrual cycles were regular at twenty-eight day intervals lasting five to six days with only a moderate flow. Dysmenorrhea was usually present. There was no intermenstrual bleeding. The patient had had but one pregnancy seven years previously, terminated after a long labor by forceps delivery. Periodic bleeding occurred throughout the entire pregnancy.

Physical examination revealed a normal female. Pelvic examination disclosed a lacerated perineum and a moderate cystocele. The cervix was hypertrophied and scarred from a previous laceration. The anterior and posterior lips were dark red, almost port wine, in color, softened, but not pulsating. The color faded to pale pink with light pressure. Neither ulceration nor eversion was noted, and the cervical canal was patent to a sound. The uterus was enlarged to about the size of a two months' pregnancy and contained several nodular eminences. With mild traction the cervix could be drawn to the introitus.

A diagnosis of cystocele, relaxed perineum, hemangioma of the cervix, multiple uterine fibroids, and prolapse of the uterus was made. On July 5, 1946, a vaginal hysterectomy and anterior and posterior colporrhaphy were performed. Convalescence was uneventful and the patient was discharged on the tenth postoperative day.

Gross examination of the surgical specimen revealed a uterus measuring 8 by 7 by 4 cm. One myoma measured 7 cm. in diameter. The remainder of the corpus was normal. The cervix was grayish white and pinkish red in the vaginal portion. A small area of superficial erosion surrounded the external os.

Microscopic examination of the cervix revealed numerous dilated capillary spaces throughout the vaginal portion, lined with a single endothelial layer, many engorged with red blood cells. The larger spaces were beneath the squamous epithelium. Deeper in the cervix these spaces were less numerous, but some cavernous sinuses could be identified in the region of the cervical glands. The connective tissue septa separating the sinuses varied considerably in thickness. Epidermidization of cervical glands, chronic cystic cervicitis, and endocervicitis were also noted. The leiomyoma was benign but did exhibit dilated vascular spaces not compatible with a diagnosis of hemangioma.

SUDDEN MATERNAL DEATH FROM AMNIOTIC FLUID EMBOLISM*

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TO THE date of this writing eleven authentic cases of fatal pulmonary embolism by amniotic fluid have been reported. Steiner and Lushbaugh¹ were the first to describe the condition in 1941 with a report of eight cases. The same authors added two more cases in 1942.² In February, 1947, Hemmings described the eleventh case.³

The purpose in reporting this case is to further emphasize the importance of embolic phenomena from amniotic fluid as an obstetric complication worthy of serious consideration. It is also of interest to note that this case illustrates the fact that in addition to the particulate components, the entrance of a large amount of amniotic fluid itself into the circulation can result in sudden death.

Case Report

A 25-year-old white woman, gravida ii, para ii, was admitted to the Chestnut Hill Hospital at 1:00 A.M. on Jan. 6, 1947, with mild cramplike pains every five to eight minutes.

She was slightly past term, her estimated date of confinement being Jan. 2, 1947. She had had a twin pregnancy in 1944, the second child being delivered by a difficult version and breech extraction.

Labor proceeded indifferently until pains became regular by 7:00 A.M. on Jan. 6, 1947, and by 8:00 A.M. they were every two to four minutes, lasting fifty seconds. Membranes ruptured spontaneously at 8:00 A.M., and the cervix was six centimeters dilated and about one-half effaced. A single dose of Demerol (100 mg.) and scopolamine (gr. $\frac{1}{150}$) was given at this time. Labor proceeded uneventfully until 9:50 A.M., at which time a rectal examination revealed a face presentation with almost complete dilatation of the cervix. The patient offered no unusual complaints, and pains persisted at two-minute intervals, lasting sixty seconds.

Preparations were being made to transfer the patient to the delivery room when she suddenly became cyanotic, took several convulsive gasps, and ceased to breathe. A faint radial pulse was discernible after respirations ceased. All restorative measures were of no avail. Death occurred about five minutes after the onset of symptoms.

There are two points of interest in the autopsy report as given by Dr. Thomas Cope of Chestnut Hill Hospital. These are: (1) the gross findings in the genitals, and (2) the microscopic picture of the lungs. A direct transcription of these follows:

Genitals.—The uterus was enlarged so that it almost completely filled the abdomen. It contained a full-term, male fetus of estimated weight 7 to $7\frac{1}{2}$ pounds. The cervix had been effaced and completely or almost completely dilated. The baby's head was fully engaged in a face presentation so there was very considerable molding and a large degree of swelling of the chin and lower jaw. The baby was quite perfectly formed and appeared normal in every respect. It was attached by an umbilical cord of normal length to a normal placenta which was attached to the left side of the uterus. Little fluid remained within the uterus when it was opened. The muscle and decidua lining of the fundus appeared quite normal. The cervix was thinned out, dilated, and completely effaced. On the right side, 2 to 3 cm. above the cervical lip, there was a ragged tear 10 to 15 mm. across. A little blood and considerable free fluid exuded from this opening after the removal of the fetus. The opening led almost directly into the broad ligament which was enormously swollen and boggy with fluid. This swelling extended into the adjacent retroperitoneal space and up the kidney and reaching almost to the liver. All of these tissues were glistening and almost translucent with fluid. The total amount present appeared to be 500 c.c. or more.

*Presented at a meeting of the Philadelphia Obstetrical Society on October 2, 1947.

Comment

The six cases of hemangioma of the cervix reported by Machado and Junqueira were diagnosed by tissue section of surgical or biopsy specimens. Their patients complained of irregular vaginal bleeding, especially contact bleeding. Carcinoma of the cervix was suspected chiefly. The lesions described were wine colored, soft and spongy to the touch, fading on gentle pressure. Free bleeding occurred with biopsy, requiring sutures for control. Chronic cervical infection was noted in all sections and accounted for the induration upon which the suspicion of carcinoma was based. The presence of dilated venous spaces with an endothelial lining separated by septa established the diagnosis. These lesions were chiefly beneath the portio vaginalis. One patient on whom amputation of the cervix was performed subsequently was delivered of a viable fetus. No recurrence was noted at delivery, and there was no excessive loss of blood.

As in most of the cases described by Machado and Junqueira, our patient had a soft, wine colored cervical lesion, which faded on gentle pressure. Carcinoma was not suspected and a biopsy was not deemed advisable. Hysterectomy was performed because of the associated obstetric injuries and the uterine fibroid. A follow-up examination on Nov. 26, 1946, revealed no evidence of recurrence.

Summary

A patient with hemangioma of the uterine cervix diagnosed clinically because of its gross appearance was subjected to vaginal hysterectomy for associated pathologic lesions. Microscopic examination of the cervix revealed a cavernous hemangioma involving chiefly the portio vaginalis.

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pregnancy, blood pressure, urine, and circulation being within normal limits. She went into labor early in the morning; I was called, dressed, went to the telephone to call a taxicab when the telephone rang again and the nurse reported that she thought the woman was dead. When I reached the hospital I found that she was dead. I delivered a dead baby by forceps. She had not been bearing down, or rather she had just begun to bear down. No post-mortem was obtainable. The nurses stated that she had been perfectly normal up to the time they called me; that after that a nurse went back to see how she was and found her apparently dead. As a necropsy was not obtainable, the diagnosis is only provisional.

The other case was a multipara who had been in normal labor for a short time, probably a couple of hours, when I examined her and found a prolapse of the knuckle of the cord. She was immediately anesthetized and the easiest version that I ever did was performed. During this procedure she suddenly became blanched and, in spite of stimulation, she died about seven hours later. No postmortem was obtainable in this case.

Of course, as has been said above, these two cases are not proved, since there was no post-mortem examination in either case.

DR. WATKINS (Closing).—I think there are two important things we should keep in mind about this phenomenon. First is the time element. My personal feeling is that these patients die rapidly, and I am in complete agreement with Dr. Willson when he says those patients who have gone on for twenty-four to thirty-six hours probably have complicating factors involved along with the original process. Secondly, I do not believe we can make the diagnosis on any patient without accurate postmortem examination. We cannot say because we have a sudden, unexplainable death that the patient died from an amniotic fluid embolus unless the microscopic pulmonary pathology is clearly demonstrated.

Lungs.—The general structure was normal, although some of the air spaces appeared large and occasional loose ends of alveolar wall suggested rupture of the elements. On the other hand, there were many small areas in which the lung appeared compressed which appearance by the presence (generally throughout the tissues but especially in these areas) of numerous intra-alveolar macrophages laden with yellowish brown and black pigment granules. These resembled heart failure cells very closely but appropriate stains failed to demonstrate iron in the pigment. Vessels throughout were dilated with red cells, and in some areas there was leakage with intra-alveolar hemorrhages. In many of the capillaries and arterioles there were bits of foreign material of uncertain nature. These were accompanied by considerable infiltration of leucocytes, generally within the vessel but sometimes in its walls. This reaction was similar in appearance to that illustrated and described by Steiner et al., J. A. M. A. 117: 1245, 1941.

In correlating the pathologic findings with the rapid clinical course in this case the following points should be stressed:

1. The amount of particulate matter observed in the lungs was relatively small, and in itself was probably not sufficient to cause death.
2. The amount of fluid reaching the lungs must have been great. The patient literally "drowned" in her own amniotic fluid.
3. The process of extravasation of amniotic fluid into the right broad ligament and into the venous circulation by means of the small uterine tear must have been going on for some time before the onset of symptoms.
4. The possibility that some anaphylactic or anaphylactoid reaction could be an added factor in this case is also to be considered.

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The writer wishes to express his appreciation to Dr. Paul E. Steiner and Dr. Thomas A. Cope for their cooperation in the preparation of this report.

46 E. WILLOW GROVE AVENUE.

Discussion

DR. J. ROBERT WILLSON.—It seems certain that fatal amniotic fluid emboli do occur, and the course of the embolism has been completely described by Dr. Watkins. On the other hand, I am not completely convinced that all the cases in the literature are deaths from amniotic fluid emboli. We know that chorionic epithelium is transported from the uterus to the lungs during pregnancy, and I do not believe anyone has proved as yet that the elements responsible for fatal emboli are not transported in the same manner in certain instances during labor. Careful examination of multiple sections of lungs of patients who die from other causes during or shortly after labor may demonstrate the same debris found in cases of fatal amniotic fluid emboli. In the original series of these cases reported, there were several who had very large blood losses that were not adequately replaced. I think it is not unlikely, since some of these patients survived for a considerable period of time, that the cause of death in this group was hemorrhage rather than amniotic fluid emboli. Amniotic fluid embolus is going to be a good out in the future for sudden deaths during delivery, and I think before making the diagnosis we should consider and eliminate all the other causes of sudden death which may occur during labor. The diagnosis should never be made, of course, without post-mortem confirmation of its existence and elimination of all other factors. In cases that are as thoroughly studied as Dr. Watkin's there can be no question of these other things, but we should all be very careful in assigning an obstetric death to amniotic fluid emboli unless we can be very sure there is no other reason which would leave us a little less blameless.

DR. WILLIAM R. NICHOLSON.—I have had two cases in past years that seem to me probably to fall into this category—one a multipara who had been perfectly normal during

at home four months after discharge from the Hospital, and probably also had generalized sarcomatosis, though no autopsy was secured.

Diagnosis.—The diagnosis of sarcoma was based on the classical criteria described in textbooks and articles on the subject. The clinical charts were studied and the necessary data were tabulated. In addition, all of the microscopic slides were assembled and reviewed so that the subject was considered as a whole. This was an important part of the survey and as a result two cases of highly cellular leiomyoma and two cases of mixed mesodermal tumor of the uterus were deleted from the series, leaving a total of sixteen cases. It is interesting that both deleted cases of cellular leiomyoma are still living some two years after operation, and both cases of mixed mesodermal tumor were dead about two years after the diagnosis was established.

Classification

The tumors were classified into four groups.

Group I.—Sarcoma originating in leiomyoma: Of the sixteen tumors, less than one-half (7), were recognized as leiomyosarcomas. Histologically some of them were seen to be typically arranged in whorls, but others were found accidentally in what clinically were diagnosed as fibroids, singled out by the pathologist because of the unusual gross appearance. The yellow color of the tumor was of great importance, and the fleshy, soft consistency, often accompanied by necrosis and hemorrhage, was characteristic in the gross. The microscopic picture was the final criterion. While the tumor histologically resembles the fibrosarcoma, its outstanding differentiating feature is its tendency to grow in whorls with pleomorphic cells, often rich in tumor giant cell formation. Extensive necrosis of cells away from the vascular supply was common, and the "combing out" effect around the vessels, a point so diagnostic of sarcoma, was also characteristic. Atypical mitoses were a rather constant finding.

Group II.—Sarcoma originating in endometrial stroma: Three tumors originated in the endometrial stroma. The tumors were of the round cell type and, therefore, anaplastic. Two of the cases were associated with adenocarcinoma of the uterine fundus and were reported elsewhere.⁹ Two of the three patients are dead, the third is living three years after operation. In this patient it is interesting and important to note that the sarcoma was an accidental finding in a uterus filled with leiomyomas. Round cell sarcoma originating in the stroma of the endometrium is difficult to understand. Since the endometrial stroma is said to be of connective tissue origin, the tumor originating from such a cell should be of fibroblastic origin, and, therefore, a fibrosarcoma. The characteristic cell in the tumor under discussion is a round cell and shows no fibroglia fibrils. As previously stated, it may be considered an anaplastic type of tumor.

Group III.—Sarcoma originating in the cervix: One case of sarcoma originated in the cervix. This, because of its grapelike growth, was considered to be sarcoma-botryoides in the adult. No striated muscle fibers nor other cellular abnormalities were found in this tumor. It recurred and finally proved fatal about a year after initial diagnosis. This grapelike sarcoma of the cervix is more rare in adults than it is in children, and represents the only primary sarcoma of the cervix seen at the Magee Hospital in twenty-five years.

Group IV.—Miscellaneous: The fourth group includes five cases. One rare type involved the uterine wall diffusely. It was an undifferentiated growth, a simple sarcoma of the uterine wall. The entire uterus was large and diffusely infiltrated with the growth. There were also small leiomyomas that were uninvolved. This patient lived about five years after the diagnosis was made. Following hysterectomy she seemed well for almost four years, and then developed a metastatic mass in the right upper quadrant. She was given x-ray therapy, and a resection of the colon was performed in an attempt to eliminate the metastases. Three months before her death she was again given 6200 r over six areas, but finally succumbed.

The second patient presented an anaplastic growth which began in a fibroid and later diffusely involved the uterus and cervix. Two cases were unclassified. One of these showed extensive metastases from sarcomatous growth taken at random from the uterus, and the other was one that showed an anaplastic sarcoma in what seemed grossly to be a fibroid.

SARCOMA OF THE UTERUS*

Review of Cases at the Elizabeth Steel Magee Hospital

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A REVIEW of the records at the Elizabeth Steel Magee Hospital for the twenty-five year period from November, 1920, to June, 1945, disclosed 16 cases of histologically proved sarcoma of the uterus in 23,859 gynecologic cases. In the same period there were 607 cases of carcinoma of the uterus, 173 occurring in the fundus, and 434 in the cervix. There were 2,017 fibroid tumors. The incidence of sarcoma was one in 38 malignancies of the uterus including body and cervix (2.6 per cent). and one to 126 fibroids (0.79 per cent).

The variations found in reported series of incidence of sarcoma in malignant disease of the uterus are as follows: Novak,¹ 4.5 per cent; Randall,² 8 per cent; Scarlight,³ 2 per cent; Goldberger,⁴ 3.5 per cent; Evans,⁵ 2.5 per cent; Veit,⁶ 2.6 per cent; Danforth,⁷ 5.5 per cent; Curtis,⁸ 2 per cent; Magee Hospital, 2.6 per cent. The highest was 8 per cent, the lowest 2 per cent.

Clinical Data

The average age of the Magee series of patients was 46 years. The youngest was 26 and the oldest was 73 years. Six of the sixteen patients were more than 50 years old. Five had been delivered of children and one had aborted three times. Ten patients had never been pregnant. Six had undergone menopause. Four were spinsters. Fourteen were white and two were Negro.

Vaginal bleeding was the most common symptom, occurring in nine cases. Other symptoms varied. Loss of weight was present in only two, pain in the lower abdomen in six, profound weakness in only two. Dyspareunia and purulent discharge occurred once only.

Fibroid tumor of the uterus was present in ten patients, four of whom were unmarried. Metastases were found in five cases, three at operation and two at autopsy, with the lungs, liver, and kidneys being involved in one, and all of the organs of generation in the second.

X-ray examination of the chest and pelvis done in five patients failed to disclose any evidence of metastases.

Clinical diagnosis preoperatively included malignant tumor, ovarian cyst, degenerating fibroid tumors, submucous fibroid, and carcinoma of the fundus.

Treatment.—Panhysterectomy was done in five patients. Five had supravaginal hysterectomy, and three of these patients also received follow-up roentgen therapy. Three were treated solely with radium following diagnostic curettage, and one with roentgen therapy only. One received no operative treatment except biopsy of the cervix to confirm the diagnosis; exploratory laparotomy only was done in one patient. One patient was treated solely with roentgen therapy and transfusions of whole blood and plasma.

Follow-up.—Eleven patients are dead. Five are living and apparently well. In the five surviving patients the sarcoma was an accidental finding and was discovered as a result of gross and histologic study of the removed tissue. The intervals since operation for the living patients were one, three, eight, and fifteen years.

Eight patients, or 72 per cent, died in the first, one in the second, one in the fourth, and one in the fifth year after admission to the Hospital. All died of generalized sarcomatosis, but in one the supplemental diagnosis of influenza was made. This patient died

*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Jan. 12, 1948.

†Died June 28, 1946.

POSSIBLE HEMOLYTIC ANEMIA OF THE NEWBORN DUE TO HIGH TITER ANTI-"A" AGGLUTININ IN A GROUP "O" MOTHER

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MRS. L. S., aged 22 years, para 0, gravida i, a white woman of Italian extraction, first seen on Aug. 22, 1946, had her last menstrual period on Jan. 13, 1946, giving her an expected date of confinement of Oct. 20, 1946. Her past history was not remarkable, except for diphtheria in childhood, for which she received at least eight intramuscular injections of whole blood without any apparent ill-effect, and for which her father and his brother were the donors. Her antepartum course was not remarkable. The patient's blood type was "O," the Rh factor was positive, and her hemoglobin was 11.8 Gm. (Sahli). The father was typed recently and found to be type "O," Rh positive, of the subgroup Rh₁ and heterozygous, but his brother was dead.

On Oct. 13, 1946, after a labor of twenty hours and twenty-two minutes, she was delivered at 11:20 A.M. of a 6 pound 2 ounce baby boy, 17 $\frac{3}{4}$ inches long, from left sacroanterior position, frank breech, by breech extraction and the Wigand-Martin maneuver with the aid of a right mediolateral episiotomy. The baby cried spontaneously and appeared to be normal.

About six and one-half hours after delivery the baby was placed in an incubator and given oxygen because of its dusky color, but examination by a pediatrician revealed no abnormal findings other than slightly diminished breath sounds at the left lung base. On the following morning, October 14, the baby's hemoglobin was 16.1 Gm., the red blood count was 4.1 million, the white count was 23,000, polymorphonuclears 75 per cent, lymphocytes 21 per cent, monocytes 4 per cent, and 10 nucleated red blood cells were found. The blood type was "A" and the Rh was positive. The pediatrician who examined the child this day noted that the spleen was palpable and the baby was a little jaundiced. It appeared to be a thirty-eight weeks' gestation. He suggested the possibility of erythroblastosis fetalis and advised prophylactic transfusion. The baby was accordingly transfused on October 15 with 75 c.c. of type "A" Rh-positive whole bank blood, five days old. Prior to transfusion on October 15, the hemoglobin was 16.5 Gm. and the red blood count was 4.20 million, white count 25,000, with a normal differential and 10 nucleated red blood cells still present.

Two days following transfusion, on October 17, the hemoglobin was 21 Gm., the red blood count was 5.26 million. The next day, October 18, the hemoglobin had fallen to 16.5 Gm. with a red blood count of 4.1 million, white count 23,000, with no nucleated red blood cells. Six days following transfusion, October 21, the hemoglobin had fallen to 15.1 Gm., the red blood count to 3.5 million, and, because of this, the baby was given a transfusion on October 22 of 75 c.c. of type "A" Rh-negative whole bank blood, seven days old. Despite this transfusion and the clinical improvement of the baby, two days after the second transfusion, October 24, the hemoglobin was 14.9 Gm., the red blood count was 4.96 million. Six days following the second transfusion, October 28, the hemoglobin was 13.6 Gm. and the red blood count was 4.46 million, but the baby was in good condition and the jaundice, which had been present, had entirely cleared so that further transfusion was delayed. Since its condition continued to improve and it gained weight, going from 6 pounds to 6 pounds 4 ounces on October 31, its eighteenth day, no further transfusion was given. On the twenty-second day after birth, November 4, the hemoglobin had risen to 15 Gm. with a red blood count of 5.01 million. The baby was discharged home in good condition on its twenty-fourth day, November 6, weighing 6 pounds 9 $\frac{1}{2}$ ounces, 7 ounces above birth weight.

On the basis of red blood counts, this baby showed no real anemia, the counts being above four million, with one exception when it was 3.5 million (Table I). However, the hemoglobin determinations (Sahli method) may indicate a slight anemia, since they fell from

Still another case was extraordinary. When first seen, the patient was in the third trimester of pregnancy. She had enormously enlarged breasts which proved to be involved in changes associated with sarcoma of the vulva, cervix, uterus, and ovaries. This was apparently a vivid example of the rapid stimulation of tumor growth during pregnancy. There were widespread metastases and death. During life the diagnosis was established by cervical biopsy. At autopsy it was not possible to identify the original site of the tumor, although it may have been the ovary. The growth was anaplastic and undifferentiated and, most remarkably, involved all of the organs of generation.

Summary

1. A twenty-five year survey of the gynecologic service at the Elizabeth Steel Magee Hospital yields sixteen cases of sarcoma of the uterus, giving an incidence of 2.6 per cent of all malignancies of the uterus. The comparative incidence of sarcoma of all fibroid uterine tumors in this series was 0.8 per cent.

2. Only seven of the sixteen were histologically leiomyosarcomas, and ten of the sixteen originated in fibroids. Three originated in the stroma of the endometrium, and can be considered round cell sarcomas.

3. Five of the sixteen patients are still living, and longest survival period being fifteen years. It must be remembered that in all of the five surviving, sarcoma was an accidental finding in uteri removed for fibroids.

4. In one case of sarcoma complicating pregnancy the metastases were extensive and rapid.

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Addendum

Since this paper was written one case of leiomyomasarcoma uteri has been found.

The patient was 53 years of age, white, married, who gave a history of menopause two years previous to admission. About three to four months later she developed post-menopausal vaginal bleeding and had several episodes since then. She lost 37 pounds in weight in the past six months. Lower abdominal pain has been present for the past ten years. She has had 15 children.

She was admitted on May 8, 1947, and was operated upon May 13, at which time a supravaginal hysterectomy, removal of cyst of mesentery, and lysis of adhesions between caecum and uterus were performed.

X-ray of chest on May 22, 1947, showed no evidence of parenchymal or bone metastases.

She had five doses of x-ray therapy beginning July 15 and discontinued on August 4 because of her clinical condition. She died on August 24, 1947, of generalized sarcomatosis, partial intestinal obstruction, and peritonitis.

No autopsy was performed.

Reviewing the blood work of this case, Diamond³ states, "As regards the average anti-"A" titer of nonpregnant women and of men, it usually varies between a dilution of 16 and about 500 at a maximum. However, gravid women, particularly of Group "O" or Group "B," who are pregnant with "A" children, often show a rise which is probably not important clinically. The maximum figures we have found in such patients have seldom exceeded 5,000. We have a few instances of a titer as high as 100,000 without clinical disease in the baby. Certainly the figure of several million is a most unusual one and is quite consistent, or, in fact, even convincing evidence of the mild hemolytic anemia which the child had."

This anti-"A" titer of 82 million is the highest that I have been able to find in the literature.⁴ In a later communication, Diamond stresses the point, "that the level of agglutinin is no index as to how much harm the baby will sustain whether it is anti-Rh, or anti-"A," or anti-"B."

Fifteen months after birth this baby is alive and well and has progressed normally and has no apparent sequelae from its mild hemolytic anemia.

This case is being reported to record a possible case of mild hemolytic anemia of the newborn caused by a high titer anti-"A" agglutinin in a Group "O" mother with a Group "A" baby.

All the special blood work in this case was done by the Blood Grouping Laboratory of Boston, Massachusetts, and received the special attention of Louis K. Diamond, M.D., who devoted much time and care to the analysis of this case, and to whom special thanks are given.

W. F. Watton, M.D., the pediatrician in the case, is thanked for his cooperation and for the excellent care of the child.

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an initial 16.1 Gm. to a low of 13.6 Gm. during the first fifteen days post partum, despite two whole blood transfusions. The temporary nature of the rise in hemoglobin following the first transfusion and the lack of response to the second, plus the failure to maintain a hemoglobin level, give rise to the suspicion that some process in the baby was destroying red blood cells.

TABLE I

| DATE 1946 | AGE IN DAYS | HEMO- GLOBIN GRAMS (SAHLI) | RED BLOOD CELLS (MIL- LIONS) | LEU- CYTES | POLYS | LYMPHS | MONO | EOSIN | NUCLE- ATED R.B.C. |
|--------------|-------------------|--|--|---------------|-------|--------|------|-------|--------------------------|
| Oct. 14 | 1 | 16.1 | 4.10 | 23,000 | 75 | 21 | 4 | 0 | 10 |
| Oct. 15 | 2 | 16.5 | 4.20 | 25,000 | 56 | 40 | 2 | 2 | 10 |
| Oct. 15 | 2 | Transfusion 75 c.c. Type "A" Rh Positive Whole Bank Blood, Five Days Old | | | | | | | |
| Oct. 17 | 4 | 21.0 | 5.26 | --- | | | | | |
| Oct. 18 | 5 | 16.5 | 4.10 | 23,000 | 68 | 27 | 4 | 1 | None |
| Oct. 21 | 8 | 15.1 | 3.50 | --- | | | | | |
| Oct. 22 | 9 | Transfusion 75 c.c. Type "A" Rh Negative Whole Bank Blood, Seven Days Old | | | | | | | |
| Oct. 24 | 11 | 14.9 | 4.96 | --- | | | | | |
| Oct. 28 | 15 | 13.6 | 4.46 | --- | | | | | |
| Nov. 4 | 22 | 15.0 | 5.01 | --- | | | | | |
| Nov. 6 | 24 | Discharged Home | | | | | | | |

Because of the possibility of a mistake in the determination of blood types, blood specimens of the father, mother, and baby were sent to a research laboratory where the following findings were reported, which were in agreement with the original typings that were done:

"Mother: Group "O," Rh Positive of the Subtype Rh₁, and heterozygous.

Father: Group "A," Rh Positive of the Subtype Rh₁, and heterozygous.

Baby: Group "A," Rh Positive of the Subtype Rh₁, and heterozygous."

In 1936 Jonsson¹ reported that a mother of blood Group "O" may develop a higher titer of anti-"A" agglutinin if she is carrying a fetus with the "A" agglutinin than if the fetus were Group "B" or Group "O." C. A. Smith² notes that "Such a development would of course render her a most unsuitable donor for transfusion of blood to her infant, and thus offers one more reason for careful crossmatching of bloods in transfusion to the newly born patient." Because of Jonsson's findings, specimens of the mother's blood were sent to a research laboratory, starting October 28, the fifteenth postpartum day when the anti-"A" agglutinin level had an end point in saline at a dilution of 1:1,000 and in albumin about 1:2,000. On the fortieth postpartum day, Nov. 22, 1946, the end point of the anti-"A" titer was 82 million in saline and albumin.

Further specimens were sent to this research laboratory, and on Jan. 22, 1947, the report states: "Exhaustive tests were performed on the serum in an effort to demonstrate that the mother had an immune type of anti-A agglutinin, which might have been stimulated by a Group A baby. We were unsuccessful in proving this, although once more we find a relatively high titer of anti-A agglutinin, which may or may not be significant in presupposing that the baby had mild anemia due to the action of anti-A on its A cells." It was suggested that another test be done on the mother's blood in about a year to determine the level of the anti-"A" titer.

Accordingly, on Nov. 17, 1947, thirteen months post partum, a specimen of the mother's blood was again tested and the anti-"A" titer was found to have an end point of 4,000 in saline and albumin as compared with 82 million on Nov. 22, 1946. Because of this it is felt that this was possibly a case of mild hemolytic anemia of the newborn due to specific stimulation by the "A" baby on the "O" mother.

was exquisite tenderness in the right lower quadrant at the level of the umbilicus and none over the region of the kidneys. Rectally, the presenting part was at zero to minus one station and the cervix was well effaced but not dilated. A catheterized urine specimen was negative. A complete blood count revealed 3,420,000 red blood cells, 12,600 white blood cells, 73.2 per cent hemoglobin, 6 stabs, 84 segments, 9 small lymphocytes and one monocyte.

The preoperative diagnosis was twisted ovarian neoplasm, or acute appendicitis complicating pregnancy at term. A laparotomy was performed through a high gridiron incision, five hours after the onset of symptoms. About 100 to 150 c.c. of turbid fluid were aspirated from the peritoneal cavity. The appendix appeared indurated, was covered with a thick purulent exudate, and was fixed behind the cecum at the level of the right posterior iliac crest. An appendectomy was done and the abdomen closed in layers without drainage.

The pathologic diagnosis, as reported by the pathologist, was acute suppurative appendicitis and periappendicitis.

The immediate postoperative condition was satisfactory. An initial dose of 100,000 units of penicillin was followed with 40,000 units intramuscularly every three hours. Other supportive measures included intravenous fluids, sedation and Wangensteen suction.

At 6:30 P.M. on Nov. 17, 1946, thirty hours after surgery, the membranes ruptured spontaneously. Uterine contractions at five-minute intervals began two hours later. Rectal examination at the time revealed no cervical dilatation and station of minus one to zero. 1,000 c.c. of 5 per cent glucose in saline intravenously, two doses of 100 mg. of Demerol and $\frac{1}{150}$ grain of scopolamine each, plus oxygen inhalation were administered during the next twelve hours. The cervix was completely dilated and the presenting part came down to a plus one station at about 7:00 A.M. on Nov. 18, 1946. At 8:00 A.M., after one hour in the second stage, the presenting part came down to a plus two station. The condition of the patient and the fetus appeared satisfactory. Under nitrous oxide-oxygen anesthesia, a deep mesiolateral episiotomy was followed by rotation of the occiput from a right occipitoposterior to a right occipitoanterior position with Kielland forceps. A Simpson forceps was then applied and a 7 pound, 15 ounce, living, male infant was delivered. The placenta soon followed and the episiotomy was repaired.

The patient did generally well except for a temperature rise to 101.6° F., four hours after appendectomy and another rise to 102° F., twenty-four hours after delivery. 500 c.c. of whole blood were given on the fourth postpartum day to overcome a moderate anemia. She was discharged from the hospital five days after delivery. She could have remained in the hospital a few more days but the obstetric floor had to be cleared because one of the mothers had developed chicken pox. She refused transfer to another floor and insisted on going home. Re-examination one week and five weeks later revealed that the patient and baby were enjoying excellent health.

Comment

The case presented adds further proof that prompt operative intervention is most imperative in suspected appendicitis complicating pregnancy near term. The classic symptoms of acute appendicitis as given in most surgical textbooks were not present in this case. The onset was with pain in the right lower abdomen and mild nausea. No other symptoms developed. Yet, acute suppurative appendicitis with considerable peritoneal response was found within five hours after the onset. There is no doubt that further procrastination might have been hazardous for the patient as well as for her baby.

The end result in our case speaks favorably for the method of prompt appendectomy and allowing the pregnancy to take its natural course.

Summary

1. The patient whose case is presented had an acute suppurative appendicitis and periappendicitis complicating pregnancy at term.
2. Appendectomy was performed five hours after the onset of symptoms.
3. The fetal membranes ruptured spontaneously and labor began thirty hours after surgery.

ACUTE SUPPURATIVE APPENDICITIS AND PREGNANCY AT TERM

SAMUEL J. TURNER, M.D., AND MANUEL B. WEISS, M.D., CHICAGO, ILL.

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ACUTE appendicitis is a relatively uncommon and very serious complication when occurring during pregnancy at term. The incidence based on case reports as presented by Baer, Reis, and Arens,¹ Cosgrove,² Norton and Connell,⁴ Meiling,³ and Priest⁶ varies from one to three for every ten thousand births.

All authorities agree that immediate surgical intervention is the treatment of choice and may be a lifesaving measure for the mother as well as for the infant. However, the surgical procedures advised meet with considerable controversy. Baer, Reis, and Arens,¹ Cosgrove,² Norton and Connell,⁴ Te Linde,⁷ Titus,⁸ Priest,⁶ and Stauder⁹ advise immediate appendectomy with great caution so as not to interfere with the pregnancy at the time of operation. The end results obtained by these authors justify their conclusions. During the past two years, others have been advocating a much more radical approach. E. M. C. Passos,⁵ quoted by Greenhill, prefers an appendectomy and a simultaneous delivery of the baby through the lower passages in multiparous women where the cervix can be dilated by accouchement forcé. In primiparas, he advises cesarean section prior to appendectomy. Meiling³ urges termination of pregnancy by transverse laparotrachelotomy followed by appendectomy in all cases of acute appendicitis during the last two months of gestation. Post-operatively, he advises the use of massive doses of sulfonamides and antibiotics.

It is because of the existing disagreement in the management of this serious complication of pregnancy that the following case is considered worth reporting.

Case Report

M. M. (History No. 155720), 22-year-old married, white woman, para 0, gravida i, was admitted to the hospital at 8:20 A.M. on Nov. 16, 1946, two weeks before the expected date of confinement. The patient stated that, after an uneventful night, she awoke voluntarily at 5:30 A.M. to prepare breakfast. About 6:00 A.M., after urinating without any pain or discomfort, she suddenly experienced a severe, stabbing pain in the right lower quadrant of her abdomen. This colicky pain recurred at intervals of three to five minutes, and partial relief was obtained by lying on her back and keeping her right thigh flexed upon her abdomen. She was slightly nauseated, but did not vomit.

The prenatal history revealed a last menstrual period on Feb. 24, 1946. Her family history was negative. She had a noncomplicated mitral regurgitation which gave her no cardiac difficulties. The blood pressure remained normal at 120/70 and the total weight gain was 23 pounds. She had an acute upper respiratory infection during the third month and an acute right pyelitis during the eighth month of gestation. Pelvimetry revealed a medium-sized gynecoid type of pelvis. A complete blood count was within normal limits, the Kahn reaction was negative, the Rh factor was positive, and urinalysis was normal at all times, except that it was loaded with pus cells for several days during the time she had pyelitis.

Examination upon admission to the hospital disclosed a well-nourished, 22-year-old, white woman, lying on her back keeping her right thigh somewhat flexed upon her abdomen, with a general appearance of being uncomfortable but not acutely ill. Temperature was 99.2° F., pulse 90 and blood pressure 120/80. The eyes, ears, nose, and throat were negative. The breasts and lungs were normal. The heart had a loud systolic murmur at the apex which was transmitted to the axilla. The abdomen appeared to be the size of a full-term pregnancy. The height of the fundus was 38 centimeters, the position of the baby right occipitotransverse and the fetal heart sounds were of good quality. Uterine contractions were not present. There

Department of Reviews and Abstracts

Selected Abstracts

Abortion

Canna, S.: Prematurity and Abortion During War Time, *La Ginecologia* 13: 515, 1947.

Stillbirths, incidence of prematurity, and abortions in a consecutive series of 6,000 deliveries are reported by Canna, including pre- and war-time cases.

During the period covering the years 1933-1939 (prewar period), cases of abortion accounted for 12 per cent of the total number of observed pregnancies, whereas, during the period covering the years 1942-1945, the abortion rate rose to 15 per cent. This increase affected primiparas and multiparas. In primiparas the rate increased from 4 per cent to 7 per cent; in multiparas from 6 per cent to 20 per cent. Agricultural laborers showed the highest increase.

Prematurity and stillbirths also showed an increase during the war of from 13.8 to 21.8 per cent of the total number of pregnancies. Increase was highest in factory workers.

Canna attributes the increase in abortions mainly to the very definite increase in syphilitic infections observed during this period and the increase in prematurity to the heavy factory work to which the women were not accustomed. GEMMA BARZILAI.

Analgesia

Rogers, Walter C.: Spinal Anesthesia in More Than Five Thousand Vaginal Deliveries, *West. J. Surg.* 236: April, 1948.

The widely accepted thesis that spinal anesthesia is dangerous in obstetrics is strongly denied. The procedure was used in 5,067 deliveries. Advantages over general anesthesia are: mothers awake and cooperative, relaxation of cervix and perineum, patient quiet during episiotomy repair, more rapid postpartum recovery, and low incidence of narcotized babies. A few serious anesthetic reactions are reported in this series but these occurred early in the experience before the author had learned to keep the dose low. Headaches following spinal anesthesia continue to be an annoying side effect, occurring in about 10 per cent of the cases. There were no maternal deaths and no fetal deaths attributable to the anesthesia.

Administration of the anesthetic agent in a hyperbaric solution is strongly recommended, the preferred drug being Pontocaine in a dose of 3 mg. to 10 mg. in a 2 per cent glucose solution. WILLIAM BICKERS.

Cesarean Section

Adama, Theodore W.: A Statistical Review of Two Hundred and Forty-One Consecutive Cesarean Sections, *West. J. Surg.* April, 1948, p. 243.

A cesarean incidence of 7.9 per cent in a series of 3,045 deliveries managed in private practice is reported by the author and justification for the high incidence is presented. In

4. Delivery of a living, seven pound, fifteen ounce, male infant was accomplished through the lower passages forty-four hours after appendectomy.
5. Mother and baby left the hospital in good condition five days after delivery.

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30 NORTH MICHIGAN AVENUE.

Bourne, Aleck: Endocrines in Gynaecology, Brit. M. J. 4489: 79, 1947.

Bourne reviews the progress in this field of medicine since its initiation by Stockard and Papanicolaou in 1917. The present-day concept of the physiology of the various hormones is first discussed. He postulates the existence of receptor substances in the vaginal mucosa, endometrium, and other tissues in the genital tract which are able to react with the estrogenic molecule and, by chemical or other union, perform a specific function. The absence of such substance in other tissues of the body is obvious. The author stresses the fallacious conclusions with reference to human physiology that are often drawn from animal experimentation.

In approaching the problem of therapeutics, he stresses the lack of exact knowledge as to whether we are dealing with a deficiency, excess, or disordered rhythm in the production of the hormones concerned. In the evaluation of therapeutic response he suggests dividing the sex-organ disabilities into those which are functional and those which are objective or organic. In the latter group, the only one in which we can be certain of success is in suppression of lactation. The results of treatment in pelvic hypoplasia with amenorrhea and sterility, atrophy of vulvovagina, leucoplakia, and metropathia have been disappointing. Likewise the treatment of functional disorders such as dysmenorrhea and repeated abortion gives disappointing results.

In summary, the disappointments in therapy are attributed to plunging too quickly from the endocrinology of animals to its application in clinical medicine. Another difficulty is the complexity of biochemical assay in various organic fluids from qualitative and quantitative points of view and their impractical aspects in practice.

R. G. DOUGLAS.

Endometriosis

McGuff, Paul, Dockerty, Malcolm B., Waugh, John M., and Randall, Lawrence M.: Endometriosis as a Cause of Intestinal Obstruction, Surg., Gynec. & Obst. March, 1948.

The paper presents an analytical study of sixteen cases of intestinal obstruction caused by endometriosis. The usual symptoms of lower intestinal obstruction, associated with acquired dysmenorrhea, sterility, and pelvic pain should bring the possibility of this condition to mind. The treatment is relief of the obstruction, usually by resection. The question of removal of the pelvic organs will depend on the extent of the endometrial implants. If there is hope of future pregnancy, bilateral oophorectomy should be avoided. A plea is made for the more frequent use of frozen sections to prevent confusing this lesion with carcinoma.

LOUIS M. HELLMAN.

Gynecology

Frank, Robert T.: Dyspareunia: A Problem for the General Practitioner, J. A. M. A. 136: 361, 1948.

The author reviews his clinical experiences over a period of years in the treatment of dyspareunia. These cases represented 1.5 per cent of his gynecologic practice over the same number of years. Dyspareunia that developed with marriage was primary and when the onset occurred later it was termed secondary and treated accordingly. It was interesting to note that of the 349 patients reviewed, normal pelves were noted in 63 patients. Fifty-five per cent of these women showed neuroses and psychoneuroses, in sharp contrast to the percentage of the total figure (349) which was only 25 per cent. The husband problem predominated in 36 cases. In primary and secondary dyspareunia, local therapy combined with enlightenment and orientation proved effective.

WILLIAM BERMAN.

Norment, W. B.: A Method of Study of the Uterine Canal, South. Surgeon, Dec., 1947.

Direct visualization of the uterine cavity and x-ray hystrogram are advocated for the study of gynecologic patients. For hystrogram study, and organic iodine in alcohol by Rayopake is recommended in preference to oil. Direct visualization of the uterine cavity is obtained by the insertion of a translucent and transparent bag over a plastic cannula which is inserted into the uterine cavity.

the total series of patients, the method of delivery was: spontaneous delivery 18.3 per cent, low forceps 61.2 per cent, midforceps 3.8 per cent, breech extractions 3.4 per cent, versions and extractions 0.3 per cent, craniotomy 0.03 per cent, and cesarean section 7.9 per cent.

The laparotrachelotomy was a favored operation, the classical operation being employed only in specific indication. Cesarean hysterectomy was used 22 times, 4 for Couvelaire uterus, 2 in uterine atony, and 2 in uterine infection. The remaining Cesarean hysterectomies were done because of large fibroids.

The high incidence of cesarean section here reported is justified on the basis that, while a single specific indication for the operation is not always present, there was in every case one or more obstetric or medical complications, the sum of which was sufficient to justify the procedure. In 34.4 per cent of the sections, the indication was previous cesarean section. Placenta previa in which bleeding was above minimal was considered adequate indication: those showing evidence of prenatal separation of the placenta were likewise submitted to section unless the cervix was partially dilated by the patient already in labor. There were seven women with definite heart disease in the cesarean group, and no maternal or fetal death, which makes one surmise that the heart disease was not of the severe type. The toxemias did not provide an indication. There were no maternal deaths, an incurred mortality of 0.8 per cent, and a morbidity rate of 49 per cent. It is believed that the final judgment upon the obstetric ability of an operator should be based upon maternal and fetal mortality, with less attention paid to his cesarean incidence.

WILLIAM BICKERS.

Endocrinology

Rakoff, A. E.: The Endocrine Factors in Pelvic Tumors With a Discussion of the Papanicolaou Smear Method for Diagnosis, Radiology 50: 190, 1948.

The author reviews the literature concerning the various clinical findings relative to ovarian dysfunction and cancer of the uterus. He also reviews the experimental work on the carcinogenic effect of estrogens.

In his study of the vaginal smear method of diagnosis of cancer, Rakoff believes that the procedure is sufficiently worth while to be made a routine part of the examination. He also states that a goodly percentage of cancers can be missed from a single examination. Endometrial cancers are harder to detect by the smear method than cervical cancers. The author feels that the best procedure is to take smears from both the cervix and the vagina for the most accurate diagnosis.

WILLIAM BERMAN.

Marrian, G. F.: The Corpus Luteum Hormone, Edinburgh M. J. 54: 611-619, 1947.

Progesterone is produced by the corpus luteum, or by the placenta after the twelfth week of pregnancy. Metabolic conversion occurs mainly, but not exclusively, in the endometrium. The chief urinary metabolite is sodium pregnanediol glucuronate, the amount of which can be estimated by weighing the purified salt, or by a more sensitive colorimetric determination of pregnanediol freed by hydrolysis. Since pregnanediol is also a metabolite of desoxycorticosterone and possibly other steroids, and, since it is not the only metabolite of progesterone, we cannot assume a quantitative relationship between endogenous progesterone production and pregnanediol excretion.

Urinary pregnanediol appears 24 to 48 hours after ovulation, and rises to a maximum level of 2 to 8 mg. per day in the late cycle. In early pregnancy, excretion averages 10 mg. per day, but soon after the tenth week the value begins its climb to about 75 mg. per day, with an abrupt fall at parturition. Stilbestrol administration increases pregnanediol excretion during pregnancy, and may be of value in preventing abortion, premature labor, and toxemias of pregnancy.

Pregnanediol determinations may be used to diagnose anovulatory menstrual cycles, and as a rapid pregnancy test.

IRVING L. FRANK.

formed transperitoneally: 1, mobilization of the rectum and suture of the transversalis fascia; 2, closure of the pouch of Douglas; 3, fixation of the pelvic colon to the lateral wall of the pelvis. The operation has been successfully performed on four patients. LOUIS M. HELLMAN.

Shaw, Henry N.: Prolapse of the Vaginal Vault Following Hysterectomy: A New Method of Repair, West. J. Surg. 56: 127, 1948.

Prolapse of the vaginal vault following total hysterectomy is the result of poor surgical technique. Failure to suture the broad ligament, uterosacral and uterovesical ligaments into the vault will often be followed by this unfortunate sequel.

Various methods have been described for replacing the prolapsed vagina: suture to the presacral fascia, the use of fascia lata loops, abdominal fixation, and the LeFort operation. There are reported successful operations upon three patients with vaginal prolapse by the use of fascia strips from the anterior rectus sheath. These strips were brought down extraperitoneally and sutured to the vaginal vault, thus maintaining the vagina in its normal anatomical relation.

WILLIAM BICKERS.

Mammary Glands

Davison, T. C., and Letton, A. H.: Testosterone in Far Advanced Breast Cancer, South. Surgeon 14: 170, 1948.

Ulrich first reported the treatment of breast cancer with androgen. Adair and Herman have contributed to the study by further publications. Androgens apparently delay or retard the cellular activity particularly of the metastatic neoplastic cell. Recalcification of bone in the site of metastases has been observed and biopsy of metastatic region following treatment with 50 mg. of testosterone daily reveals some fibrosis about the neoplastic cells with apparent inhibition of nuclei activity in the malignant cells.

Eight patients are reported. The first had a mastectomy for cancer followed by x-ray therapy and subsequently developed metastases of the ilium. Calcification of the ilium occurred following testosterone therapy. The second case had a somewhat similar history and the vaginal smear showed evidence of estrogenic activity. Following testosterone therapy there was partial recalcification of the right ilium and she gained weight. The third patient had metastases to the rib and lung and her vaginal smear showed marked estrogenic activity. Large doses of testosterone failed to change the picture in this case.

Case 4 was similar, but there was marked regression of rib metastases following testosterone and the patient returned to full improvement and was comfortable for a long period. The other four cases showed similar response to treatment.

Seven of eight patients had some pain relief and gained weight on testosterone therapy. Four patients with extensive metastases were able to return to work. One patient who had tissue metastases only had an excellent result for over fifteen months. The best results are found in patients who show evidence of estrogenic depression. Poorer results are shown in those who show persistent estrogenic activity. Masculinizing effects are noted, to which patients do not object, since they realize the gravity of their condition and are grateful for the relief of pain.

WILLIAM BICKERS.

J. B. Enticknap: Angioblastoma of the Breast Complicating Pregnancy, Brit. M. J. 4462: 51, July 13, 1946.

This case is reported because of the rarity of the condition, the fact that this type of tumor complicating pregnancy has not previously been reported, and the unusual degree of malignancy. The general incidence is probably about 0.1 per cent of breast tumors and only about one-third of these are malignant.

When three months pregnant, a twenty-year-old primipara noticed a hardness developing in her left breast. When she was admitted to Charing Cross Hospital three months later, the

The author now uses a transparent plastic sheet with a cannula attached to the optic instrument for obtaining photographs of the uterine cavity. He reports a satisfactory visualization of intrauterine pathology with this instrument.

WILLIAM BICKERS.

Charles, A. H.: A Case of Hydatidiform Mole at Age 52, *Brit. M. J.* 4473: 460, 1946.

The case is reported because of the advanced age of the patient. In a review of the literature, twenty pregnancies in women of 50 years of age were found, five of whom had moles. The condition is encountered two and one-half times more frequently in women over 40 years of age. Most authors favor hysterectomy in this age group because of the incidence of chorionepithelioma following the condition. The case report concerns a 52-year-old woman who had vaginal spotting for 2 months. A dilatation and curettage was done and the pathological examination of the tissue interpreted as carcinoma. A second curettage in another institution revealed the true nature of the condition. A complete hysterectomy and bilateral salpingo-oophorectomy were done. The suspected pathology was confirmed and the subsequent course was uneventful.

R. G. DOUGLAS.

Gynecologic Operations

Smith, George Van S., and Mulligan, William J.: Dicumarol Prophylaxis Against Venous Thrombosis in Women Undergoing Surgery, *Surg., Gynec. & Obst.*, April, 1948.

This paper is a progress report on the administration of Dicumarol prophylactically to 2,353 operative patients at the Free Hospital for Women. The objective of this therapy was the reduction of the incidence of postoperative embolic phenomena. This seems to have been accomplished, for the incidence of thrombic complications in the four-year period prior to therapy was 1:90, while, in a similar period during which the patients were treated with various dosage schedules of Dicumarol, the incidence fell to 1:138. The authors point out the necessity of following the patients with prothrombin levels in order to secure adequate therapeutic results.

LOUIS M. HELLMAN.

Reiner, Walter C.: Gigantic Ovarian Cyst Developing in a Thecoma, *West. J. Surg.*, April, 1948, p. 205.

Large ovarian tumors have become a rarity in civilized countries. The author reports a case of thecoma with cystic changes. The patient, aged 62, was admitted to the hospital because of a large abdominal mass, edema of the ankles, dizziness, and a bloody vaginal discharge of four years' duration. She was emaciated, the hemoglobin was 47 per cent, the urine contained a trace of albumin and a moderate number of red blood cells. She was given frequent small feedings of nourishing food, supplemented with cerivamic acids and vitamin K and liver extract. At the initial operation, an incision was made into the cyst and a tube inserted. Six thousand cubic centimeters of dark brown fluid were drained slowly. She was then returned to her room where the tumor was slowly depressed over a period of three days. At the end of this time, the tumor was removed with great difficulty, because of many adhesions to all of the abdominal organs.

Pathologic examination revealed a solid tumor having the appearance of a thecoma surrounded by huge areas of cystic degeneration. The patient made an uneventful recovery. The total amount of fluid removed was 26,500 c.c., the weight 60.1 lb.

WILLIAM BICKERS.

Dunphy, J. Englebert: A Combined Perineal and Abdominal Operation for the Repair of Rectal Prolapse, *Surg., Gynec. & Obst.*, April, 1948.

An operation for complete rectal prolapse is described. This is not an original procedure but a combination of various techniques described by others and involves: 1, circular amputation of the prolapsed segment of rectum; 2, excision of the redundant hernial sac; 3, suture of the levators anterior to the rectum, all from below. The following are then per-

tologically, with the exception of invasion, the anaplastic epithelium is distinguishable from noninvasive carcinoma. Nuclear measurements were done and the nuclear volume for anaplastic and carcinoma cells was similar, both being much greater than that for normal cervical epithelial cells.

It is thought that anaplasia of the cervix may be the precursor of invasive carcinoma. In other studies, follow-up of patients showing these epithelial changes has shown that a high percentage of them develop invasive carcinoma.

WILLIAM BICKERS.

Hill, Wm. Harry, and Glenn, Wadley R.: Multiple Pelvic Malignancies, *South. Surg.* 14: 192, 1948.

Multiple primary malignancy arising in the different organs of the same patient is sufficiently rare to be noteworthy.

A case is reported of a 57-year-old white woman who was admitted with a history of intermittent bloody diarrhea. Examination revealed a normal cervix but the pelvis was frozen and the anterior vaginal fornix filled with a firm fixed mass. Rectal examination revealed a palpable rectal lesion. Diagnosis of pelvic malignancy with obstruction and metastases to the bowel was made. The patient showed signs of intestinal obstruction. At operation, a bilateral pseudomucinous cystadenocarcinoma of the ovary was found, and, at the rectal sigmoid junction, there was a primary annular carcinoma. The pathologic report confirmed the clinical impression that the two malignancies arose independently.

WILLIAM BICKERS.

Miscellaneous

Bloxson, Allan, and Matthaei, Rose: An Anti-Rh Antigen-Antibody Reaction Factor (The Rh Protective Factor), *Bull. Johns Hopkins Hosp.* 82: 1, 1948.

In a preliminary article the authors show a factor in the blood of Rh-negative individuals which inhibits the reaction between anti-Rh serum and Rh-positive cells. This is said to be different from blocking antibody. The factor is present in greater strength in Rh-negative males, and the use of their blood in the transfusion of erythroblastotic infants is thought to be therapeutically beneficial. Its use in the prevention of hemolytic disease by transfusion of the mother is suggested.

LOUIS M. HELLMAN.

Reynolds, S. R. M., Heart, O. O., Bruns, Paul, and Hellman, L. M.: A Multi-Channel Strain-Gage Tokodynamometer: an Instrument for Studying Patterns of Uterine Contractions in Pregnant Women, *Bull. Johns Hopkins Hosp.*, April, 1948.

An entirely new form of multichannel tokodynamometer using 3 strain gages simultaneously is presented. An electric-spark frictionless recorded portrays graphically the contraction patterns of three different zones of the uterus during labor. Tracings of normal labor are portrayed. These show a substance of activity of the mid zone and lower segment as labor progresses. Toward the end of the first stage, there is a complete preponderance of the fundus. Records portraying the effect of small doses of pituitary extract on normal labor are also shown. The records can be analyzed for frequency, rhythmicity, total relative work per unit period of time, intensity of contraction, contraction time, contraction duration, and contraction and relaxation rates. Because of the construction of the pick-ups, the instrument permits great localization of effect. It is thus possible to demonstrate the gradual emergence of the fundus as the predominating contractile force during labor.

LOUIS M. HELLMAN.

James, Hal P., Elliott, Henry W., and Page, Ernest W.: Oxygen Uptake of Human Placental Tissue as Affected by Selected Substrates and Drugs, *Society for Experimental Biology and Medicine* 67: 1948.

The effects of various drugs on the oxygen uptake of the term human placenta was studied. The CO_2 was depressed by the Demerol, Amytal, scopolamine and diethylstilbestrol. Morphine had no effect. The drug concentrations used were all in excess of the therapeutic dosage.

LOUIS M. HELLMAN.

tumor measured 72 cm. in circumference. Clinical signs of infection were present. Radiation therapy was started. Biopsy was negative for neoplastic cells and aspiration yielded blood. Amputation was decided upon because of anemia, hemorrhage into the tumor, and ulceration. Local recurrence appeared in the scar but resolved with radiotherapy. Recurrences again developed and disappeared with therapy. Delivery was uncomplicated at term and the patient died two months post partum with evidence of metastases. The tumor removed weighed 2,400 Gm., was 75 cm. in circumference, resembled organized blood clot on cross section, and microscopically was classified as an angioblastoma. R. G. DOUGLAS.

Malignancies

Posey, Louis C., and Cunningham, Joseph A.: Impressions of the Vaginal Smear Technic in the Diagnosis of Cervical Cancer, *South. M. J.* 41: 217, 1948.

The vaginal smear for the diagnosis of uterine cancer is technically simple but requires considerable time for examination of the smear and skillful interpretation of vaginal cytology. The cancer cell shows a cellular pleomorphism and basophilia which is a function of the rate of cell growth. In slow-growing malignant tumors, these findings may be absent, thus making interpretation difficult. Another note of warning is sounded on the basis that desquamation of tumor cells is a function of surface area and rate of growth and, therefore, cancer with small surface area and slow growth may desquamate sparingly and thus increase the error in diagnosing from the vaginal smear. In acute infection superimposed upon the cancer site, the exudate may dilute the desquamated cells and, being highly cytotoxic, may bring about desquamation of the malignant cells prior to exfoliation. It is felt that the smear method as a satisfactory screen method test for cancer is yet to be established. WILLIAM BICKERS.

Speck, George: A Clinical Review of Papillary Adenocarcinoma of the Ovary, *Virginia M. Monthly*, April, 1948, p. 185.

Carcinoma of the ovary makes up approximately one-third of all ovarian neoplasms. Thus, the frequency is second only to malignancies arising in the cervix and corpus uteri. Papillary adenocarcinoma is the most common of the malignant tumors of the ovary. Early signs and symptoms are absent, thus bringing most patients to diagnosis late in the disease.

It is thought that the tumors arise from the germinal epithelium covering the ovary. They usually arise bilaterally or, at the time of operation, are usually found bilaterally. Pathologically, the different diagnosis between benign and malignant papillary tumors of the ovary may be quite difficult. Indeed, pathologists do not agree on cytologic criteria for the different diagnosis. The surgeon is left with the responsibility of treating all papillary tumors of the ovary as malignant neoplasms. Radical surgery is necessary because of extensive lymph drainage from the ovary and the tendency of these tumors to metastasize the tubes and uterus. It is generally conceded that the cure must depend almost entirely upon surgery, as radiation therapy offers little in the way of improving the survival rate. Prognosis for the papillary adenocarcinoma is grave. The gross extent of the lesion and the histologic appearance of the tumor influence the survival rate. The best five-year survival thus reported is 50 per cent in a group of patients in whom the lesion was small, limited to one ovary, and apparently removed completely at operation. The overall survival rate for all patients with papillary adenocarcinoma probably does not exceed 5 per cent. WILLIAM BICKERS.

Ashworth, C. T., and Diddle, A. W.: Anaplastic Cervical Epithelium, *South. M. J.* 41: 217, 1948.

The histologic characteristics of sixteen cervixes with anaplastic epithelium have been studied and compared with those of invasive carcinoma of the cervix. The cervixes which showed anaplasia were found among 1,815 patients upon whom biopsy of the cervix was done. Anaplasia is characterized by hypertrophy, hyperchromatization, and variation in the size of the nuclei. The basement membrane is usually lobulated, although remaining intact. His-

Stillbestrol and progesterone therapy was started in the sixteenth week of gestation. Progesterone was given in a dose of 10.0 mg. two times per week and the dose increased until, at the thirty-second week, the patient was receiving 15 mg. daily. Approximately 25 mg. of stillbestrol were given daily from the sixteenth week until delivery. Hormone requirements and the effect of therapy were not checked by pregnandiol excretion studies or serum gonadotropin levels.

It is believed that all diabetic women should be delivered by the end of the thirty-sixth week of gestation. If spontaneous delivery does not occur, cesarean section is a procedure of choice.

WILLIAM BICKERS.

Matthew, G. D.: *Thrombophlebitis in Pregnancy*, *Edinburgh M. J.* 54: 641-48, 1947.

Pregnancy phenomena predisposing to thrombophlebitis are (a) elevated plasma fibrinogen, (b) venous stasis in the legs (especially with the large uteri of hydramnios or multiple pregnancy), (c) the occasional need for long periods of antepartum bed rest, (d) trauma to leg veins during labor and delivery, and (e) bacterial invasion of the physiologic thrombi in the placenta site sinuses. The incidence of thrombophlebitis is high (4 per cent) after cesarean section and difficult forceps deliveries.

In 19 cases treated with heparin, hospitalization was a week shorter than in a control series. The author suggests early exercises, massage, and heparinization as prophylaxis in predisposed women.

IRVING L. FRANK.

Pregnancy, Physiology

Hickey, M. D., and de Valera, E.: *Variation in the Titre of Rh Antibody During Pregnancy*, *Brit. M. J.* 4497: 335, 1947.

The authors record the antibody titer as determined by the conglutination method of Wiener before, and at frequent intervals during, the sixth pregnancy of an Rh-negative patient with one living child. The figures indicate that a rise in antibody titer occurred during early pregnancy followed by a fall which was attributed to absorption of the antibody by the Rh-positive fetus. Following delivery by cesarean section at the thirty-second week, there was an immediate rise in the antibody titer from 1:16 to 1:256. The baby died twelve hours after delivery despite transfusions. Blood films showed a definite erythroblastosis.

R. G. DOUGLAS.

Pregnancy, Toxemia

Bracciale, U.: *Circulating Neutrophile Stabform in Toxemias of Pregnancy*, *Archivio di Ostetricia e Ginecologia* 53: 31, 1948.

In the healthy state, only mature segmented forms of neutrophile leucocytes enter the peripheral blood; the immature stab or band form described by Schilling is an occasional finding.

Segmented forms, the mature form of neutrophiles, account normally for 60 to 70 per cent of the circulating leucocytes, and the ratio of the juvenile form, the band form in which nuclear width is approximately uniform through the entire length of the nucleus, to the mature segmented form, is in normal cases as low as 0.05 to 0.06.

Bracciale at the Lying-in Hospital in Naples examined the ratio of band-form to mature cells in 20 cases of toxemias of pregnancy in the puerperium: 12 cases of eclampsia; 6 of pre-eclampsia; 2 of abruption of a normally inserted placenta.

The ratio showed normal values in six cases. It was increased in fourteen cases. No correlation was found between severity of the toxemia and number of circulating immature neutrophiles. In three cases, however, in which the puerperium was complicated by infection,

Newborn

Franklin, Charles H.: Penicillin in Drops for Prophylaxis Against Ophthalmia Neonatorum. South. M. J. 41: 320, 1948.

A single instillation of penicillin in the conjunctival sac in the prophylaxis against ophthalmia neonatorum is evaluated. A total of 1,107 infants was studied in the nursery and in the home during the first two weeks of life. 1.1 per cent of the infants exhibited a purulent discharge in the eyes. This percentage is approximately one-sixth of that observed following the use of silver nitrate.

In the thirteen infants who exhibited a purulent discharge during their hospitalization, culture was taken in all and fifteen different organisms were isolated from the thirteen cultures. Two-thirds of the isolated organisms were staphylococci. A follow-up study was made on 952 infants (80.9 per cent) after the patients had returned to their homes, on the fourteenth and seventeenth days of life. Of these, 902 infants were reported by the Public Health Nurse as having no ophthalmic signs. The others showed evidence of conjunctival redness or watery discharge. Of those showing purulent discharge on follow-up examination, cultures were obtained in twenty-one infants and organisms were found in all except one. The total incidence of purulent discharge in the hospitalized group was 1.1 per cent on the penicillin prophylaxis as compared to 6 per cent with silver nitrate prophylaxis.

WILLIAM BICKERS.

Salmon, George W.: Airblock in the Newborn Period, New Orleans M. & S. J. 100: 253. 1947.

Airblock is a term used to designate extrapulmonary vesicular air. Too often, death occurring in the neonatal period is attributed to small areas of atelectasis, though it is well known that several days are required for complete expansion of the newborn lung. There are good reasons for believing that aberrant air which is a common cause of neonatal death is often overlooked at necropsy. Although emphysema in the mediastinum is readily detected, air in the pulmonary vesicular areas of the lung is less readily identified. Escape of air is likely to take place when alveoli are overinflated without corresponding increase in the circumference of the underlying vessels. Artificial respiration, particularly with positive pressure machines, can be a factor in forcing air through the alveoli. Occasionally the rupture extends to the pleura, producing a pneumothorax. More often the interstitial air travels along the pulmonary vessels to the mediastinum. From here it occasionally can extend to the cervical subcutaneous tissue.

The outstanding symptoms of airblock are dyspnea and cyanosis, reduction of the respiratory excursion with greatly increased rate, distention of the neck veins, heart sounds faint and distant; pain is symptomatic of the adult but is difficult to evaluate in the newborn. Treatment is unsatisfactory unless pneumothorax occurs, when air can be moved by needle. Excellent photomicrographs illustrate the article.

WILLIAM BICKERS.

Pregnancy, Complications

Palmer, Lester J., Crampton, Joseph H., and Barnes, Robert H.: Pregnancy in the Diabetic, West. J. Surg. 56: 175, 1948.

Following the report by Priscilla White on the improved fetal survival in diabetics by the use of ovarian sterile therapy, the authors adopted her treatment program. They had previously reported, in 1945, 68 pregnancies observed in 48 diabetic women treated with hormone therapy other than insulin, and now they took 39 diabetic women treated with stilbestrol and progesterone. In the first group, the over-all fetal survival rate was 60 per cent. The second series treated with varying dose schedules of progesterone and stilbestrol had a fetal survival rate of 76.9 per cent. There was no maternal mortality in either series.

Correspondence

Stilbestrol in Endometriosis

To the Editor:

In the section under correspondence of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, I read a letter on endometriosis by Lowell F. Bushnell of Los Angeles.

At the time that the editorial appeared a paper was being prepared on the use of stilbestrol (estrogen) for treatment of endometriosis. Dr. Bushnell states that whenever diagnosis of endometriosis is proved "... the patient be instructed never to have estrogen therapy." From our studies on endometriosis in the past ten years at Jefferson Davis Hospital we have never been able to cause endometriosis to be worse by giving large doses of stilbestrol. Stilbestrol was given in three cases of endometriosis of the incision and in three cases of endometriosis of the posterior cul-de-sac. In all cases given stilbestrol, the blue nodule disappeared and became white and hard. After stilbestrol was discontinued for twelve, eight, six, and three months, there was no recurrence of blueness or bleeding from these endometrial areas. All patients are now menstruating normally with little or no pain.

Stilbestrol has been given to approximately 60 patients with endometriosis associated with severe pains before and during menstruation, now with most gratifying results and I have never seen a case made worse. One patient had a large endometrial implant in the posterior cul-de-sac. A biopsy was taken before therapy and approximately every 30 days for four times. She was given stilbestrol, 5 mg. daily increasing 5 mg. weekly for three and one-half months. The last biopsy revealed no endometriosis. If stilbestrol caused endometriosis to become worse, then in this case endometriosis would have been present in all subsequent biopsies. Yet no endometriosis was found in any of the subsequent sections. Culdoscopic examination with a Decker's instrument revealed no pelvic endometriosis. Pelvic organs which were stuck and painful became freely movable. In another case, pelvic endometriosis was diagnosed by laparotomy and biopsy. She again had all signs and symptoms of endometriosis at approximately three months after operation. Large and increasing doses of stilbestrol were given and in four to six weeks the pelvic organs became freely movable. Stilbestrol was discontinued and menstruation began which was many times less painful. She became pregnant in about three months after stilbestrol was discontinued.

One patient with endometriosis in the posterior cul-de-sac, which was seen grossly, had been married for eleven years and had no children. She became pregnant two months after stilbestrol was discontinued.

In another case, the uterus had ruptured with resulting endometriosis eight years ago. Large doses of stilbestrol were given and she has also become free of pain which was associated with endometriosis.

A patient had one child 7 years ago and presented all signs and symptoms of endometriosis. An operation had been suggested. She was given stilbestrol up to 100 mg. daily for three months. After discontinuing stilbestrol the pelvic organs became freely movable. She is now eight months pregnant.

0.1 to 25 mg. of stilbestrol were given to 20 endometriotic cases and it caused the pain to be worse.

It might be assumed that within the next ten years stilbestrol will assume one of the most important roles in the treatment of endometriosis and might replace x-ray, surgery, and radium in 75 per cent of endometriotic cases.

One may give small doses of codeine in mild cases of endometriosis and eliminate the mild pain, but it is known that endometriosis, as a rule, grows and grows so that such therapy may give one false security and resulting more extensive endometriosis at a later date. Stilbestrol appears to be a more rational therapy for mild or severe endometriosis.

KARL JOHN KARNAKY, M.D.

HOUSTON, TEXAS.

June 23, 1948.

and penicillin and sulfonamide treatment was instituted, the band to segmented ratio reached a value of 0.97, and in two cases of puerperal eclampsia regressive features such as vacuolization concentration of the chromatin, and pyknosis were present.

These findings point to the presence of an increased stimulation of the bone marrow during pregnancy.

GEMMA BARZILAI.

Radiation

Del Regato, J. A.: The Role of Transvaginal Roentgentherapy in the Treatment of Carcinoma of the Cervix, Surg., Gynec. & Obst., April, 1948.

The author reports the use of a special speculum and moderately low voltage x-ray in the transvaginal treatment of carcinoma of the cervix. He claims a lower incidence of complications if this method is used as an adjunct to external pelvic irradiation. In 76 patients with all types of cervical carcinoma there was a 44 per cent three-year survival.

LOUIS M. HELLMAN.

Kaplan, Henry S., Wilson, Hugh M., and Morse, Arthur H.: Results and Causes of Failure of Radiation Therapy in Carcinoma of the Cervix, Surg., Gynec. & Obst., March, 1948.

A small series of 88 patients with carcinoma of the cervix, treated with combined x-ray and radium, is reviewed. There is a total 38 per cent five-year survival with a 61 per cent salvage in stage I. While this compares favorably with other reports, the survival rates in stages III and IV were very low.

LOUIS M. HELLMAN.

Sterility, Fertility

Hoffman, Eugene F.: Semen Evaluation and Fertility, West. J. Surg. 56: 155, 1948.

A fertile semen specimen has the following characteristics: alkaline reaction, at least 3 c.c. in volume, grade 3 or better in motility, 60,000,000 or more per c.c., and 20 per cent or less in abnormal form. There are very few pus cells and no red blood cells in the normal specimen. There are summarized the observations made upon 495 patients.

Of this group, 27 per cent met the requirements for a normal seminal fluid described above, whether or not treated. Eighteen per cent were found to be relatively infertile but refused treatment. The remaining 55 per cent underwent treatment. In the group, there were 22 per cent who, on two or more examinations, had azoospermia which did not respond to any type of treatment. Thirteen of this group had an obstructed vas, eight had atrophic testes following mumps, and in the remaining patients no pathology could be demonstrated. In the group whose specimens showed only relative infertility, there were 35 who were still infertile when treatment was stopped, 46 who showed no improvement in the treatment, and 76 who showed improvement but were not able to impregnate their wives. There were 57 of the 495 patients who succeeded in impregnation, one of these with a seminal count which never exceeded 2,000,000 per c.c. A relatively large number of the patients with defective seminal fluid had seen military service in the South Pacific where heat, humidity, exhaustion, and poor food would seem to be the contributing factors. Many men, however, associated their infertility with having been in proximity to radar equipment. There was no evidence to support this assumption.

WILLIAM BICKERS.

Necrology

JENNINGS CRAWFORD LITZENBERG, B.A., M.D., a member of the Advisory Board of the JOURNAL since its founding, professor emeritus and former head of the Department of Obstetrics and Gynecology at the University of Minnesota, author and teacher, died at the age of 78 years at his home in Minneapolis, from coronary occlusion, on Aug. 15, 1948. Dr. Litzenberg was prominent in the development of maternity care in the upper midwestern states, a member of the national and local medical societies, a past president of the American Gynecological Society, faculty counselor for twenty years of the Alpha Omega Alpha Fraternity, and a founder of the Minnesota Medical Foundation.

GEORGE L. STREETER, M.D., former director of the Department of Embryology of the Carnegie Institute of Washington and noted for his many contributions in this field, died of a heart attack in July, 1948, at the age of 75 years.

Dr. Streeter was graduated from the College of Physicians and Surgeons of Columbia University in 1899, served on the faculty of the Wistar Institute, Philadelphia, and then as professor of anatomy at the University of Michigan from 1907 to 1914. Coming to the Carnegie Institute, he developed the world-renowned collection of human embryologic material and wrote extensively for many publications.

Condylomata Acuminata

To the Editor:

A pregnant woman had verruca acuminata (condylomata acuminata). As treatment she was given two injections of neoarsphenamine. Subsequently she developed encephalopathy and came under the management of Kantor and Levin. Their diagnosis was arsenical encephalopathy (AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, August, 1948). Seven months after delivery the patient still had distressing neurological residuals.

A simple painless cure for condylomata acuminata is to paint them with a 25 per cent suspension of podophyllin in castor oil. This will cause the growths to disappear completely in several applications (depending on their extent) leaving the skin unaffected. However, the medicine must be applied to the growths only and not to the surrounding skin.

This treatment which deserves to be better known is superior to excision or cauterization under local or general anesthesia. It is certainly superior to the many nonsurgical remedies, such as application or injection of this or that substance (see any textbook) which turns out on trial to be questionable or worthless.

CHESTER D. BRADLEY, M.D.

2914 WEST AVENUE,
NEWPORT NEWS, VA.
AUG. 21, 1948.

Erratum

In the article, "The Hydrostatic Bag in Obstetrics," by N. S. Assali and R. W. Kistner, in the October issue of the JOURNAL, on page 787, in Table VI, at the top of the page, the words "Dilatation" and "Bleeding" are reversed. "Bleeding" should precede the first line of figures, and "Dilatation," the second.

American Urological Association

The American Urological Association offers an annual award of \$1000.00 (first prize of \$500.00, second prize \$300.00 and third prize \$200.00) for essays on the result of some clinical or laboratory research in Urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Biltmore Hotel in Los Angeles, May 16-19, 1949.

For full particulars write the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis 3, Tenn. Essays must be in his hands before February 15, 1949.

The Twelfth British Congress of Obstetrics and Gynaecology

To be held in the Friends Meeting House, Euston Road, London, in July, 1949.

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| <i>President:</i> Sir Eardley Holland. <i>Hon. Secretaries:</i> A. Joseph Wrigley. Ian Jackson. | } | 58, Queen Anne Street, (Royal College of Obstetricians & Gynaecologists) London, W.1. |
|---|---|---|

WEDNESDAY, July 6.

Morning Session.—(Chairman: The President)

The Congress will be declared open by the Minister of Health.

“Modern Caesarean Section.” Introduced by Mr. McIntosh Marshall (Liverpool).

Afternoon Session.—

(1) Guest Paper. Dr. Joe Meigs (Boston, Mass.).

(2) “Pregnadiol.” Introduced by Prof. C. F. Marrian (Edinburgh) and Dr. G. I. M. Swyer (London).

THURSDAY, July 7.

Morning Session.—

“Essential Hypertension in Pregnancy.” Introduced by Prof. George Pickering (London) and Prof. F. J. Browne (London).

Afternoon Session.—

(1) “Hernia of Pouch of Douglas.” Introduced by Mr. Charles Read (London).

(2) “The Management of Pregnancy in Diabetics.” Introduced by Mr. John Peel (London) and Prof. D. M. Dunlop (Edinburgh).

FRIDAY, July 8.

Morning Session.—

“Diagnosis and Prognosis of Carcinoma of the Uterus.” Introduced by Dr. J. E. Ayre (Montreal), and Dr. Spears (Cambridge).

Afternoon Session.—

Discussion on Maternal Mortality.

Owing to the difficulties that exist at the present time in arranging hotel accommodation, travel, etc., the Hon. Secretaries would like to have the names of those who hope to attend, by March 31, 1949, at the latest, and, if possible, very much before that date.

Items

American Board of Obstetrics and Gynecology

The following physicians are to be included in the list of diplomates certified by this Board:

Brown, Hunter Merrill, 1922 South Tenth Avenue, Birmingham, Alabama, born 1909, received M.D. from Tulane University in 1934.

Magee, Thomas Lea, II, 578 Polk Street, Monterey, California, born 1908, received M.D. from Stanford University in 1939.

Stowe, Lyman M., New Haven Hospital, New Haven, Connecticut, born 1914, received M.D. from Yale University in 1938.

PAUL TITUS, M.D., Secretary.

American Board of Obstetrics and Gynecology, Inc.

A number of changes in Board requirements and regulations were made at the annual meeting of the Board held in Washington, D. C., May 16 to May 22, 1948. New Bulletins are now available for distribution upon application and give details of all new regulations. These relate both to candidates and to hospitals conducting residency services for training.

Foremost are the following:

(1) The ruling that applicants must receive adequate training in both obstetrics and gynecology has been defined as meaning a minimum of six months, full-time, in the branch of either obstetrics or gynecology relegated to a minor role in a candidate's training and preference for practice.

(2) Acceptable preceptorship training is defined.

(3) The present regulation requiring at least six months of practice in the specialty following the completion of an acceptable training period, has now been extended, effective Dec. 31, 1949, to a requirement of two years post-training practice limited to the specialty.

(4) Specific requirements for approval of hospital services for residency training are outlined.

(5) Effective immediately, there will be no further temporary approvals of hospital services for residency training. It is planned that all hospitals holding any type of residency training approval will soon either be resurveyed or initially surveyed by the Council on Medical Education and Hospitals of the A. M. A. so that all future approvals, new or old, will be based entirely upon inspection following application. It is expected also that certain resurveys will result in withdrawal of present residency approval from institutions where the educational and training standards are not being maintained.

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 4, 1949. Application may be made until Nov. 1, 1948. Application forms and Bulletins are sent upon request made to

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY,
1015 HIGHLAND BUILDING,
PITTSBURGH 6, PA.

tomy by the vaginal route has not been employed because of its neglect of the glandbearing area, and I personally have had no experience with the operation.

From a perusal of the records of the Chelsea Hospital for Women, it appears that the first radical abdominal hysterectomy for carcinoma of the cervix was performed by Bonney in 1907, and it must be remembered that at this time there was no adequate alternative method of treatment. The operation was performed with increasing frequency up to the late 1920's, by which time radiotherapy, with its low mortality and increasing efficiency, in part, supplanted surgery as a method of treatment. I feel, however, that in the present state of our knowledge there is still an important place for surgery in the treatment of carcinoma of the cervix, and my colleagues also believe this.

In his "all out" surgical attack on carcinoma of the cervix, Victor Bonney, between the years 1907 to 1936, performed 500 consecutive Wertheim operations. He has since passed the 600 mark. He operated upon all cases which were technically removable with the exception of a few in whom was present some condition which contraindicated operation. He began his series in 1907, when no other effective method of treatment was available and he continued throughout to operate on all operable cases. His operability rate so far as could be judged was 63 per cent of all cases seen, and his series included Stage I, II, and III growths. Unfortunately, analysis of the stage of advancement of the growth cannot be made, as this classification was not in existence over the greater part of his series. He found malignant involvement of the regional glands in 40 per cent of patients operated upon, and of the 500 patients subjected to surgery there were 70 operative deaths, a mortality of 14 per cent over-all.

In my submission, this work of Bonney's represents one of the most valuable clinical research investigations ever made in respect of carcinoma of the cervix. Not only does it show what surgery alone can do in such cases, but it has afforded us the first statistical evidence on a large scale of the incidence of malignant gland involvement. It has also shown that gland involvement is not absolutely dependent upon the stage of the growth in the cervix. While it is generally true that the more advanced the growth the more likely are the glands to be affected, this is by no means always the case, and advanced cases with little or no gland involvement have been frequently encountered, while conversely, some early cervical growths have shown extensive gland invasion.

Of the 500 operations, histologic examination revealed that in 300 patients the glands were free of growth, and in 200 the glands were involved. The five-year cure rate in the gland-free cases was 53 per cent, but when corrected, 58 per cent, and the corresponding cure rate in the gland positive cases was 22 per cent, or when corrected, 23 per cent. It is thus obvious that the prognosis is gravely affected by the presence of carcinomatous deposits in the regional glands. His over-all five-year cure rate is 41 per cent of the patients operated upon.

It must be appreciated that these figures for surgery apply only to the 63 per cent of cases which are deemed to be technically operable. There remains the further 37 per cent of patients who are beyond the hope of radical surgical extirpation of the growth, or in whom age and cardiac or renal insufficiency makes operative treatment inadvisable.

American Journal of Obstetrics and Gynecology

VOL. 56

DECEMBER, 1948

No. 6

Original Communications

THE ROLE OF SURGERY IN THE TREATMENT OF CARCINOMA OF THE CERVIX*

CHARLES D. READ, M.D., LONDON, ENGLAND

I SHOULD, at the outset, like to express my appreciation of the honor you have done me in inviting me to take part in the evening's proceedings of this famous Society. I am deeply conscious of that honor, and my pleasure is the greater in that the subject under review is one which has interested me deeply. Coming as I do from the Chelsea Hospital for Women in London, I may claim to have served my apprenticeship in the Hospital in England which, led by those great surgical giants, the late Sir John Bland Sutton, the late Sir Comyns Berkeley, and Mr. Victor Bonney, can claim to have consistently led an all out surgical attack on the problem of gynecologic cancer in general, and of carcinoma of the cervix in particular. It is only in recent years that radiotherapy has modified this "all out" attack, and may I state initially that we still believe that some selected cases of carcinoma of the cervix are best treated by surgical methods.

In any discussion on the subject of the treatment of carcinoma of the cervix, division of opinion invariably centers around the relative merits of radiation and radical surgery. This generally applies only to cases coming within the category of Stages I and II. There is agreement that almost all Stage III and IV growths are unsuitable for treatment by radical surgery, though even in these it is possible to treat some by a combination of surgery and radiation. We have been interested in this respect in the recent publications of Dr. Meigs of Boston and of Dr. Taussig on the relative merits of the Wertheim operation and of pelvic lymphadenectomy, respectively, and it is upon these two aspects of the subject that I wish to speak in the main.

In many clinics the Wertheim operation was abandoned when radiotherapy in the form of radium application and deep therapy became generally established, but at my hospital the radical surgical operation has been practiced continuously, but in carefully selected cases only. The Schauta hysterovaginec-

*An address read, by invitation, at a meeting of the New York Obstetrical Society, March 9, 1948.

NOTE: The Editors accept no responsibility for views and statements of authors as published in their "Original Communications."

TABLE IV. MARIE CURIE HOSPITAL (HURDON) 1942. RADIUM AND X-RAY THERAPY RESULTS. CANCER OF CERVIX

| CLASSIFICATION | STAGE I | STAGE II | STAGE III | STAGE IV | TOTAL |
|------------------------------|---------|----------|-----------|----------|-------|
| No. examined | 40 | 174 | 455 | 167 | 836 |
| No. treated | 40 | 174 | 455 | 138 | 807 |
| 5-year survivals | 32 | 107 | 143 | 10 | 292 |
| Died of cancer | 6 | 65 | 308 | 127 | 506 |
| Died of intercurrent disease | 2 | 2 | 4 | 1 | 9 |

TABLE V. MARIE CURIE HOSPITAL—LONDON (HURDON), 1942
FIVE-YEAR SURVIVAL RATE—CARCINOMA OF CERVIX

| | STAGE I | STAGE II | STAGE III | STAGE IV |
|----------|-------------|---------------|---------------|--------------|
| Relative | 80 per cent | 61.5 per cent | 31.4 per cent | 7.2 per cent |
| Absolute | 80 per cent | 61.5 per cent | 31.4 per cent | 6 per cent |

TEN-YEAR SURVIVAL RATE

| | STAGE I | STAGE II | STAGE III | STAGE IV |
|--|---------------|---------------|---------------|------------|
| | 63.6 per cent | 41.9 per cent | 22.4 per cent | 2 per cent |

The latest results published show an improvement in these figures when compared with the figures shown previously. More recently Richards of Toronto has published comparable results for radiotherapy.

From the foregoing, even the most biased surgical enthusiast must admit that over all and in general the results of radiotherapy are superior to those of surgery, in respect to operative mortality, possibly survival, but in spite of either method of treatment a considerable proportion of patients die from the disease. The problem now arises, can we salvage the lives of any of those patients who are destined to die even after adequate radiotherapy? In addition, is it ever desirable to employ surgical means without previous radiotherapy?

In a survey of the statistics relating to carcinoma of the cervix at the Chelsea Hospital for Women over the past twelve years, I find that the operation has been performed on 96 occasions, and that eight patients did not survive the operation, an operative mortality rate of 8.3 per cent. Further investigation reveals that this represents 14 per cent of all the patients presenting themselves with the disease. The highest operation rate in any one of these years was 20 per cent, and the lowest 9 per cent. Before the year 1936 on an average 55 per cent of the patients so presenting were treated by the Wertheim operation with an operative mortality of roughly 14 per cent. The year 1936 is taken as the dividing line, as it was in this year that the majority of the members of the Honorary Staff of the hospital decided to be more selective in their indications for the radical operation. It is interesting to note that just about 50 per cent of the mortality in the recent twelve-year period has been incurred by the few colleagues who have not been so selective in their indications for surgery. Had this careful selection been exercised, it is fair to assume that the operative mortality would have dropped to about 4 or 5 per cent.

This is in accordance with Dr. Meig's experience. Indeed, he published 91 consecutive operations without a postoperative death. My colleague Frank Cook and I, working independently at the Chelsea Hospital for Women and in our

Bonney's figures of 14 per cent operative mortality are constantly quoted, but it must ever be remembered that this is a mortality rate resultant from an "all out" surgical attack on practically every technically removable growth. A further analysis of his figures shows that his operative mortality in the gland-free group is 10 per cent, whereas the gland involved group showed a figure of 20 per cent.

I quote these figures not because I consider the radical abdominal operation in general to be the best method of treatment of cervical cancer but because I wish to stress the results which surgery alone can accomplish in curing the disease.

A further analysis of Bonney's results, taking into consideration the 37 per cent of patients not subjected to surgery, shows an absolute cure rate of 25 per cent, or when corrected, 26 per cent. He estimates that if the proportion of cases favorable for radiation but unfavorable for surgery because of cardiac or renal disease or adiposity be added, his absolute total saving of life should be in the region of 30 to 31 per cent.

In none of Bonney's cases was radiotherapy employed routinely either before or after operation.

At this juncture it is interesting to compare the results which were being obtained by radiotherapy. The first reliable published results appeared between 1931 to 1933 (Table I). The five workers depicted publish a total of 2,583 patients treated up to 1926 with 614 five-year survivals, i.e. a survival rate of 23.8 per cent.

TABLE I. RADICAL ABDOMINAL HYSTERECTOMY (BONNEY). 500 CASES—1907 TO 1936

| | | | |
|------------------------------|-------------------------------|----------------------------|-------------|
| <i>Operability rate</i> | 63 per cent of all cases seen | | |
| <i>Operative mortality</i> | 70 | 14 per cent | |
| Gland free group | 300 | <i>Operative mortality</i> | 10 per cent |
| Gland involved group | 200 | <i>Operative mortality</i> | 20 per cent |
| Percentage gland involvement | 40 per cent | | |

TABLE II. RADICAL ABDOMINAL HYSTERECTOMY (BONNEY). 500 CASES—1907 TO 1936

| | |
|--|-------------|
| <i>Cure rate—5 years—all cases</i> | 40 per cent |
| Corrected cure rate | 43 per cent |
| <i>Cure rate, gland free cases</i> | 53 per cent |
| Corrected cure rate | 58 per cent |
| <i>Cure rate, gland involved cases</i> | 22 per cent |
| Corrected cure rate | 23 per cent |
| <i>Absolute 5-year cure rate</i> | 25 per cent |
| but if cases favorable to radiation but unfavorable to surgery be added, he estimates the total saving of life to be 30 to 31 per cent | |

TABLE III. RADIUM RESULTS PUBLISHED, 1931 TO 1933

| YEAR | WORKER | PATIENTS | 5-YEAR SURVIVALS | PER CENT |
|------|-----------------------------------|----------|------------------|---------------|
| 1931 | Healey (U.S.A.) | 1,574 | 352 | 22.3 |
| 1932 | Regaud & Lacassagne (France) | 317 | 107 | 33.7 |
| 1933 | Gray Ward & Farran (U.S.A.) | 343 | 85 | 24.7 |
| 1933 | Kelly (U.S.A.) | 349 | 70 | 20 |
| | Total patients treated up to 1926 | 2,583 | | |
| | Total five year survivals | 614 | | 23.8 per cent |